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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: Diabetic peripheral neuropathy (DPN) is one of the most important risk factors of diabetic foot ulcers (DFU), and early screening and treatment of DPN is crucial. The Ipswich Touch Test (IPTT) is a new method for screening for DPN and, compared with traditional methods, is more simple to operate and requires no equipment. However, the screening accuracy of IPTT in DPN patients has not been well characterized. We aim to conduct a systematic review and meta-analysis to characterize the sensitivity and specifity of IPTT compared to tradition methods and to understand the potential screening value of IPTT.

Design： Systematic review and meta-analysis.

Data sources： PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Database (CBM) up to April 16, 2020.

Methods: Sensitivity, specificity, and other measures of accuracy of IPTT for screening DPN were pooled. Subgroup and sensitivity analysis were performed to identify the sources of heterogeneity. The protocol was registered with PROSEPRO (42020168420).

Results: Of 441 records retrieved, seven studies were evaluated for the screening value of IPTT. Five studies with 10g-MF as the reference standard were included in the meta-analysis, and the pooled sensitivity and specificity were 0.78 (95 % CI 0.65–0.87) and 0.95(95 % CI 0.89–0.98), respectively, and AUC was 0.93. Subgroup analysis results showed that the sample size and ethnicity were not the main sources of heterogeneity.

Conclusions: Compared with 10g-MF, IPTT displays high specificity and acceptable sensitivity as a screening tool for DPN. It can be used clinically, especially in remote areas and in primary medical

institutions, and by self-monitoring patients. More high-quality studies are needed to assess and promote more effective screening practices.

Prospero: Registration Number is CRD (42020168420)

Strengths and limitations of this study

- This is the first meta-analysis to explore the potential screening value of IPTT in DPN.
- The current evidence shows that the discrepancy between previous studies is due to the use of different reference standards by the researchers. With 10g-MF as the reference standard, IPTT displays acceptable sensitivity and a high specificity.
- Our research results are likely to have a positive impact on the screening of DPN by different medical institutions, such as in remote areas lacking equipment and personnel, and by self-monitoring patients with diabetes.
- By facilitating the identification of patients at-risk for foot ulceration, we can Effectively prevent the occurrence of DFU, and reduce the social and economic burden of this disease.
- Although we conducted sensitivity and subgroup analysis to explore the heterogeneity analysis, we were unable to determine the source of heterogeneity.

Keywords: Ipswich Touch Test, Diabetic peripheral neuropathy, Meta-analysis

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common long-term complication and the most important risk factor for the occurrence of diabetic foot ulcers (DFU).[1-4] DPN affects up to 50% of people with diabetes,[5,6] with chronic painful neuropathy affecting up to 26%.[7] In the early stage of DPN, the symptoms lack specificity, and about half of patients with diabetes cannot recognize the injury to the lower extremities.[8,9] Once the patient has symptoms such as limb numbness and pain, it signals that pathological changes have occurred in the peripheral nerves and have advanced into the

irreversible stage. If not treated promptly, serious tissue damage, such as foot ulcers, amputation, and even death, may occur.[10,11] Studies have shown that early screening and detection of peripheral neuropathy can not only slow down the DPN process, but also effectively prevent DFU.[12] Therefore, early screening and treatment of DPN is very important.

At present, the screening value of 10g monofilament (10g-MF), Vibration perception threshold (VPT), and 128Hz tuning fork in DPN has been widely recognized.[13] Compared with VPT and 128Hz tuning forks, 10g-MF is the most widely used screening tool because it is more simple, objective, and easy to carry, although it requires a calibration facility to confirm that the vertical pressure of the monofilament used when bending is 10g.[14-16] Commercially available 10g-MF devices exhibit significant variability within and between devices of different manufacturers and their actual bending force varies widely from their designated 10g value. When used they have a short service life where the instrument is within 10% of their initial bending force which is not usually the stated 10g of force.[17,18] Meanwhile, medical personnel are required to be trained before using the device, and screening is limited to hospitals or clinics. For clinics and communities in remote areas, medical personnel may lack the device or the training to screen patients for DPN, resulting in a missed opportunity for patients to receive the best treatment. In recent years, Dr. Rayman proposed the Ipswich Touch Test (IPTT), which only requires the physician's index finger. During this test, the patient is required to close their eyes while the physician lightly rests their finger on each of the patient's first, third, and fifth toes for 1 to 2 seconds. Patients are instructed to respond with a "yes" when they feel the physician's touch. Compared with the current methods, IPTT requires no equipment, and is more convenient and effective.[19] Doctors, nurses, and even family caregivers can perform the test after training.[19] It can be applied to inpatients, outpatients, community patients, self-monitoring patients at home, and to areas lacking more advanced equipment.[20,21] Currently, IPTT has been applied in some countries, and previous studies have reported differences in the results of the screening value of DPN. However, neither a meta-analysis nor a systematic review has been conducted on the screening value of IPTT.

In this study, we aimed to conduct a comprehensive and systematic literature review to systematically evaluate the potential screening value of IPTT in DPN, and provide evidence and

guidance for the clinical application value of IPTT.

METHODS

The Joanna Briggs Institute (JBI) protocol[22] has been registered with PROSPERO, the International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination (Registration Number is CRD (42020168420). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[23] statements for reporting our systematic review.

Patient and public involvement

No patient involved

Data Sources and Searches

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Biomedical Literature Database (CBM) for reports published before to April 16, 2020. For included studies with insufficient data, we emailed the authors to ask if they would provide data for our study. With this strategy, we combined search terms for applied technique (Ipswich touch test, touch test, IPTT) and disease (Diabetic peripheral neuropathy, diabetic foot, diabetic foot ulcer, Diabetes Mellitus, diabetic complications). The study design and published language was not limited. In addition, we conducted a manual search, including searching through conference papers and gray literature, and the references of all included studies were examined. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database. A detailed search strategy is provided in Appendix S1. All analyses were based on previously published studies; thus, no ethical approval and patient consent were required.

Inclusion and Exclusion Criteria

Previously published studies were included in this meta-analysis if: (1) the study was designed as a diagnostic test and systematic reviews; (2) all the research subjects were patients with diabetes, and;

(3) IPTT was included as an index test. Studies were excluded from the meta-analysis if the studies had incomplete data sets or were other than original reports (commentaries/reviews). The age, sex, region, and race of the subjects were not restricted. The published language was not limited.

Data Extraction

We imported initial search records from databases into NoteExpress V3.2.0.7535 literature management software. Two reviewers independently screened titles and abstracts of all the included literature, following the inclusion and exclusion criteria. After screening the abstract, the full text was read in detail. Any discrepancies were resolved by discussion. The following information was extracted from the eligible studies: study characteristics (author, publication year, study period, country, reference standard, setting, operators), participant characteristics (sample number, range), and outcome indicators (sensitivity, specificity, true positive number (TP), false positive number (FP), false negative number (FN), true negative number (TN)). Missing data were supplemented by contacting authors wherever possible. Data extraction was performed independently by the two reviewers. Differences were reconciled by discussion until a consensus was reached on the item in question. The methodological quality of the included studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2), as the subject of this meta-analysis is determining diagnostic accuracy.[24]

Data Synthesis

The sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and corresponding 95% confidence intervals (95% CIs) were calculated using the TP, FP, FN and TN values, which were extracted from each study prior to data pooling. The likelihood ratio is an independent indicator to assess authenticity, which can simultaneously reflect sensitivity and specificity. When the PLR is >10 or the NLR is <0.1, the probability of diagnosing or excluding a certain disease increases significantly. The likelihood ratio is more clinically significant than summary receiver operating characteristic curve (SROC) and diagnostic odds ratio (DOR) value.[25] The SROC was constructed based on a bivariate regression approach and the pooled estimate for sensitivity and specificity was subsequently calculated. The DOR with 95% CI was also calculated.

For each summary statistic, a 95% confidence interval was computed. The random effects models in meta-analysis were used to estimate variance between studies by using STATA, version15.1 (Stata Corp, College Station, TX).[26]

In addition, Fagan nomograms were generated to evaluate the clinical utility of the two screening methods. Heterogeneity among the reports was assessed by the χ2 test (Cochran Q test) and the I^2 statistic, where $p \leq 0.05$ or an $I^2 \geq 50\%$ indicated the existence of significant heterogeneity.[27] Sensitivity and subgroup analysis were performed to further determine the source of heterogeneity and to determine whether the results are stable and credible.[28] Publication bias was assessed with Egger's test. Egger's linear regression test was used to evaluate asymmetry, and $p < 0.05$ was considered to be statistically significant. All statistical tests were 2-sided.[29]

RESULTS

Study Selection

Our initial search resulted in a total of 441 records: 437 from database searching and four records from manual searches of references. After duplicates were removed, 242 records were identified, and 220 records were excluded as irrelevant.[30-34] After reading the full-text articles, 7 studies met the inclusion criteria (Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.). Two studies were excluded for lacking necessary data for meta-analysis. Finally, five studies with 6 datasets were included in the final meta-analysis, involving a total of 1162 patients.

Characteristics and Quality of the Included Studies

The characteristics of the included studies are presented in Table 1. The 7 studies included a total of 1,510 participants with diabetes and were published between 2011 and 2020. 10g-MF, VPT, NDS, pin prick, tuning fork 128Hz, and ankle reflex were used as the reference standard to explore the accuracy of IPTT in DPN. The research setting included homes of patients, clinics, care centers, and outpatient centers, and the assessors included doctors, nurses, and family caregivers.

Table 1. Basic characteristics of the included studies.

Study	Year	Country	n	Setting	operators	Reference standard	TP	FP	FN	TN	Se(%)	Sp (%)
Sharma 30	2012	UK	130	home	families	10g-MF	24	4	6	96	80.0	96.0
Sharma 31	2014	UK	331	home	families	10g-MF	65	15	18	233	78.3	93.9
				clinic	doctors/ nurses	10g-MF	67	9	16	239	81.2	96.4
Amal Madanat 32	2015	Saudi Arabia	351	care centers	doctors/ nurses	10g-MF	29	6	28	288	51.0	98.0
						VPT	48	24	9	270	85	92
						NDS	30	9	27	285	53	97
I.S, Basir 33	2020	Spain	100	care centers	doctors/ nurses	10g- MF	4	30	1	65	80.0	68.0
						Pin prick	4	1	11	84	80.0	88.0
						Tuning fork 128Hz	2	3	69	26	40.0	27.0
						Ankle reflex	1	4	2	93	20.0	97.0
Dutra 34	2020	Brasília	250	outpatient centre	doctors/ nurses	10g-MF	30	5	6	209	83.3	97.7
Rayman 19	2011	UK	265	clinic	-	VPT	-	-	-	-	76.0	90.0
Bowling 35	2012	UK	83	clinic	doctors/ nurses	VPT	-	-	-	-	100	96.6
						NDS	-	-	-	-	100	90.3

Se, Sensitivity; Sp, Specificity

We assessed the methodological quality of the studies using QUADAS-2. The risk of bias and applicability concerns were analyzed using Revman5.3. The QUADAS-2 assessment results of the research methodological quality of each study are presented in Figures 2(Figure 2. Assessment for the risk of bias) and Figure 3 (Figure 3. Assessment for the risk of bias in the included studies).

Overall, risk of bias in both groups of studies was affected by the reference standard. Different studies chose different reference standards, leading to a higher risk of bias. The second factor that led to a high risk of bias was patient selection, particularly where it was a convenience sample. In some studies, patient selection and inclusion criteria were poorly defined or unexplained. In addition, the index test is another factor resulting in a higher risk of bias, as some studies did not describe the target test in detail.

Screening Accuracy

In the included studies, the researchers used a variety of different test methods as the standard to observe the sensitivity and specificity of IPTT for screening for DPN, such as 10g-MF, VPT, NDS, tuning fork 128Hz, and ankle reflex. The differences in the sensitivity and specificity of IPTT obtained by using different test methods as reference standards are presented in Table 1. In general, when 10g-MF and VPT were used as reference standards, the sensitivity and specificity of IPTT were relatively high. For the 5 studies comprising 6 data pools that used 10g-MF as the reference standard, the sensitivity ranged from 51.0% to 83.3%,[30-34] and the specificity ranged from 68.0 to 98.0%. For the 3 studies that used VPT as a reference standard, the sensitivity ranged from 76.0 to 100.0%, and the specificity ranged from 90.0 to 96.6%. Using neuropathy disability scores (NDS) as the reference standard, Madanat et al. calculated the sensitivity of IPTT to be 0.53, and the specificity to be 0.97. Using pin prick, tuning fork 128Hz, and ankle reflex as reference standards, Basir et al calculated sensitivities of 0.80, 0.40, and 0.20, respectively, and specificities of 0.88, 0.27 and 0.97, respectively (Table 1).

Meta-analysis Results Using 10g-MF as the Reference Standard

Screening Accuracy

Six datasets were included to evaluate the overall effect of IPTT in the screening of DPN. The combined sensitivity and specificity were 0.78 (95％CI 0.65–0.87) and 0.95 (95％CI 0.89–0.98), respectively. A visual inspection of the forest plots shows large deviations and heterogeneity (sensitivity: I^2=73.57%, specificity: I^2=95.88%, p<0.01) (Figure 4. Sensitivity and specificity of IPTT in the diagnosis of DPN). In addition, the PLR was 15.5 (95％CI 7.2–33.4), the NLR was 0.23 (95％CI 0.14–0.38), and the DOR was 67 (95％CI 32–141). The SROC analysis for the studies yielded an overall weighted area under the curve of 0.93 (95%CI 0.90-0.95) (Figure 5. The SROC curve for quantitative analysis of IPTT in the diagnosis of DPN).

Subgroup Analysis and Sensitivity Analysis

The results of subgroup analysis show that sample size (n<300 or n≥300) and ethnicity (Asian or non-Asian) are not the main sources of heterogeneity (Table 2 or Supplementary Files 2). Sensitivity analysis determined a combined DOR value of 13.12, 95%CI: 10.32-16.66. After excluding each study, the difference between the combined effect and the value before exclusion was minor, suggesting the results of this study are stable (Supplementary Files 3). Fagan's analysis shows that the post-test probability of PLR can be increased by 50%, and when the pre-test probability was 94%, the NLR was reduced to 23%. The above results demonstrate that there is good diagnostic value of IPTT for DPN (Figure 6. Fagan nomogram for assessment of IPTT screening probability).

Table 2. Subgroup analysis results.

Variables	No.	Sensitivity (95%CI)	Weight(%)	Specificity (95% CI)	Weight (%)
Total	6	0.72 (0.68–0.76)	100	0.95 (0.94–0.97)	100
Race					
Asian	2	0.61 (0.34–0.87)	23.51	0.97 (0.54–1.13)	27.89
non-Asian	4	0.80 (0.75–0.86)	76.49	0.96 (0.94–0.98)	72.11
Size					
Total<300	3	0.82 (0.72–0.91)	39.43	0.89 (0.78–1.00)	42.53
Total≥300	3	0.70 (0.55–0.87)	60.57	0.97 (0.94–0.99)	57.47

Publishing Bias

The publication bias was visually presented using Egger's test. Egger's test shows p = 0.289 (95%CI:

343.8-133.42). This indicated there was no publication bias (Supplementary Files 4 Egger's test for the assessment of potential publication bias).

DISCUSSION

DPN is the most important risk factor for the occurrence of DFU and one of the more common chronic complications associated with diabetes. However, it is often ignored. Once the patient develops DPN, it is likely to cause diabetic foot ulcers, gangrene, and even amputation, and many patients experience numbness and tingling in their limbs. Early identification of DPN can greatly reduce the burden of chronic diseases on society. In this study, we systematically reviewed the relevant literature on the identification of DPN by IPTT. A total of 7 studies were included, involving 1,510 participants with diabetes to explore the value of IPTT screening. Previous studies have disputed the diagnostic value of IPTT, mainly due to the use of different test methods, such as VPT, NDS, pinprick, tuning fork 128Hz, and ankle reflex, as the reference standard.[33] Compared with NDS, acupuncture, 128Hz tuning fork, and ankle reflex, IPTT has higher screening accuracy when 10g-MF and VPT were used as the reference standard.[10,19,20] Basir et al. observed that when 128Hz tuning for was used as a reference standard, the sensitivity and specificity of IPTT was only 40% and 27%, respectively. This may be due to the fact that the predictive level of a tuning fork is less than that of the monofilament. However, Miller et al observed that combining a tuning fork with monofilament would result in a more effective evaluation.[21] Regarding the quality of the current studies, some studies lacked rigor in study design, such as the interval between target tests and unclear reference standard tests, and most studies failed to describe the reference methods in detail. The overall quality of the included studies was rated as low to medium quality.

The results of the meta-analysis found the combined sensitivity and specificity of IPTT to be 0.78 (95％CI 0.65–0.87) and 0.95 (95％CI 0.89–0.98), respectively, and AUC to be 0.93 (95%CI 0.90-0.95). The results indicated that IPTT had a moderate to high level of sensitivity and a high level of specificity for diagnosing DPN. In our analysis, a DOR equal to 1 indicated that a test was unable to distinguish between patients with or without the disease. Our study yielded a DOR value of 67

(95%CI 32–141), indicating that NLR had a certain accuracy in the diagnosis of patients with DPN. We also drew Fagan's plot, including pre-test and post-test probabilities, which describes the change to the IPTT screening of DPN. The results show that IPTT has a certain potential to improve the screening efficiency of DPN.

Heterogeneity is an important factor of this meta-analysis. To further explore the source of heterogeneity, subgroup analysis was performed based on ethnicity and sample size. However, we found that these were not a major source of heterogeneity (Table 2). Sensitivity analysis showed that the results of this study are stable, and that high heterogeneity may be a result of other factors, such as differences in research methodology, operator, and other factors. We were limited in our ability to more fully explore the sources of heterogeneity in the studies due to the underreporting of clinical variables, the limited number of reported IPTT studies, the limited overall sample size, and the presence of unclear risk of bias.

Studies have shown that routine foot examinations and rapid risk stratification are often difficult to implement in busy primary care institutions. Additionally, the lack of awareness of standardized testing for DPN amongst healthcare professionals is a concern, which may be due to a shortage of material and personnel resources in primary care institutions. This is concerning because identifying foot neuropathy and the patients at risk for ulceration has been shown to prevent the incidence of foot ulcers.[35-37] IPTT is a new method for screening DPN that does not require any tools and can be carried out after minimal training. It is not affected by time, venue, or its operators. [20] The advancement of IPTT is of great significance for the early screening of DPN to impede the progression of diabetic foot ulcers, as it can be used to quickly and reliably screen and manage patients at high-risk for ulceration, especially in remote areas or places lacking screening tools.[38,39] Kerry et al. reported that, in the first year IPTT was introduced as a screening tool, the relative risk reduction (RRR) of DFU was 64%, and in the second year, the RRR was 70%, thereby reducing hospital-acquired foot ulcers in patients with diabetes by two-thirds and negating the excess risk associated with diabetes.[40-43] Meanwhile, it can effectively improve patients' disease-related knowledge, which plays a positive role in promoting the self-management of patients and their

families. At the same time, IPTT has a predictive effect on diabetic foot ulcers and reduces delays in patient visits. [21] However, more thorough studies are needed for verification.

Most of the literature on IPTT is focused on screening tests and some commentary-type studies, and the number of studies is small. These studies were carried out in the United Kingdom, Spain, Brazil, and Saudi Arabia, and although they achieved satisfactory results, have not been carried out globally. However, it has not been applied in developing countries such as China. China is a country with a large population and a relatively small number of medical personnel, especially in some remote areas where the medical allocation is in short supply. In these areas, the application and promotion of IPTT can effectively alleviate the allocation of medical resources and play an important role in the management of patients with diabetes. IPTT has also recently been approved for use in a number of countries.[21,32-34] However, Kempegowda et al. reported that 88.4% of physicians are not familiar with IPTT. Therefore, we suggest that IPTT be further promoted amongst physicians and medical staff, especially in remote areas and areas lacking screening tools. [36] Future large-scale, high-quality, and multi-center studies on populations of different ethnicities will verify the potential applicability of IPTT alone or in combination with other DPN screening methods.

Conclusion

In summary, IPTT is a simple, novel, and straightforward method for screening DPN with high specificity and acceptable sensitivity. It can be used clinically, especially in remote areas and primary medical institutions, and self-monitoring patients. This is also the first meta-analysis of the accuracy of IPTT identification of DPN, and a systematic quantitative evaluation of its screening value, which can provide evidence for the clinical application of IPTT in the future. However, due to a limited number of studies of low or medium quality from limited geographical areas, more high-quality studies are needed to promote more effective screening practices.

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Conflict of interest

The authors state that they have no conflict of interest.

Author contributions

ZN conducted the database search, screened and extracted data for the meta-analysis, prepared extracted data for the procedures, and had primary responsibility in writing this article. LXY, ZJ and ZJ performed statistical analysis and interpretation of data. XJC, ZQH, and LJH contributed to the discussion and editing. XJC and CJR critically revised the draft manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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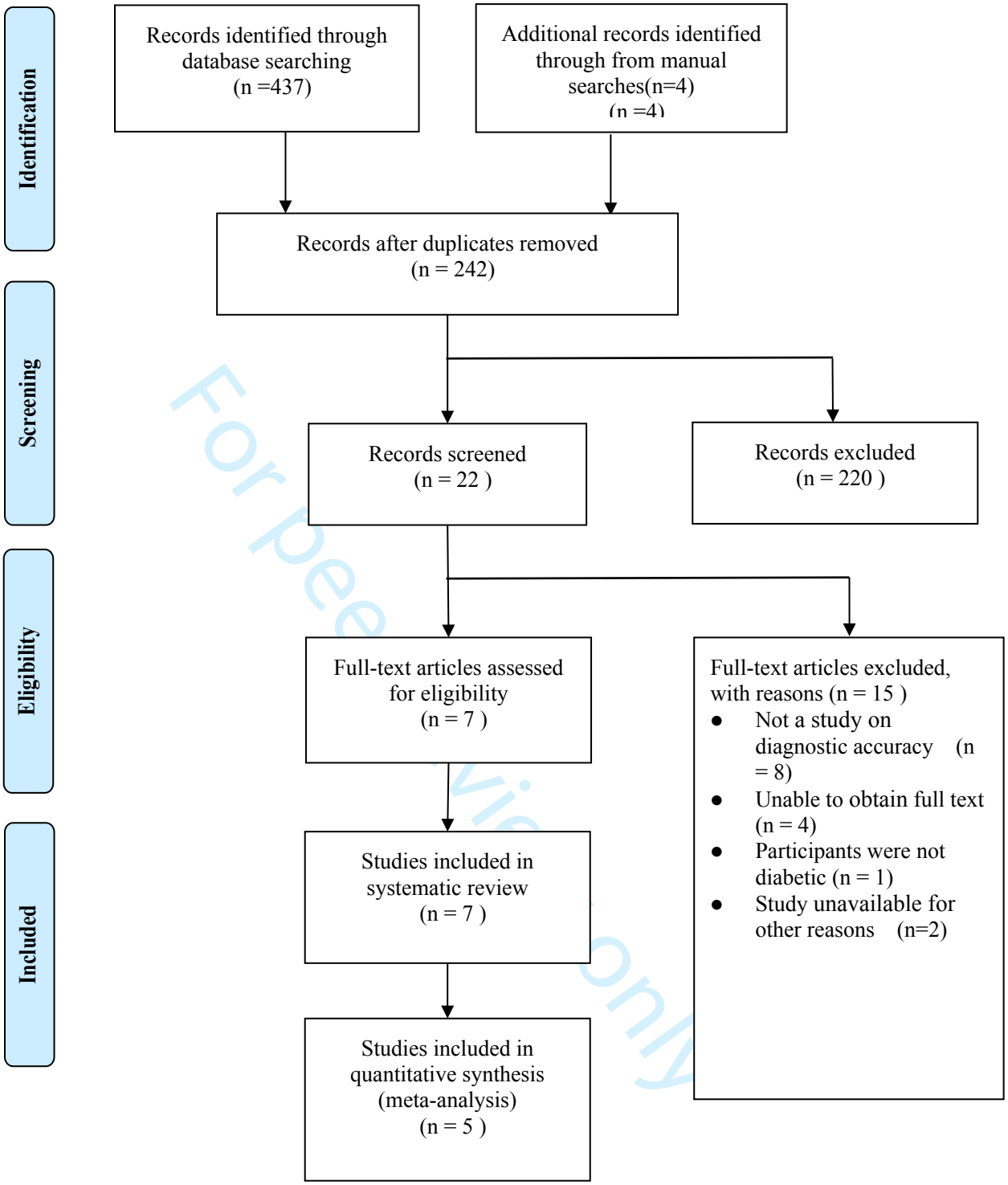

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

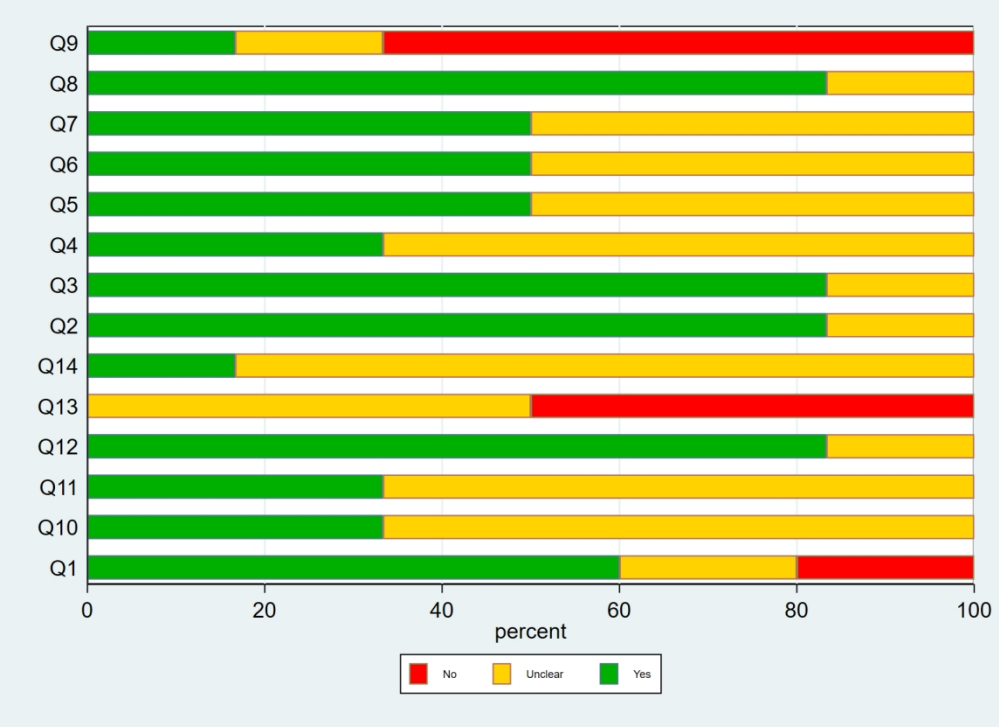

Figure 2 Assessment for risk of bias.

589x428mm (72 x 72 DPI)

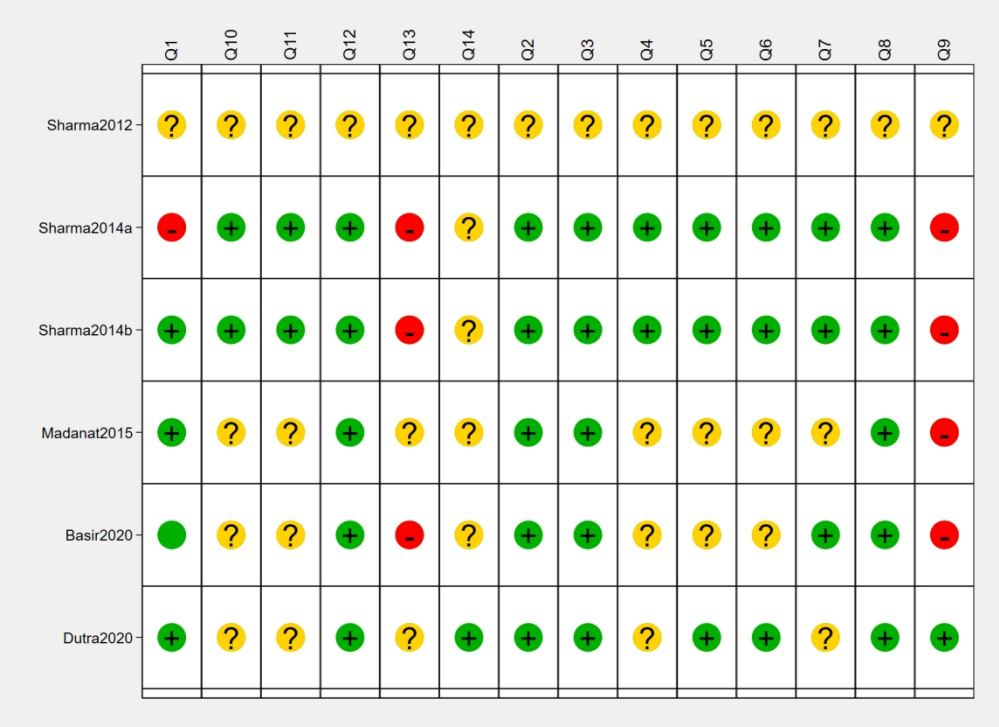

Figure 3. Assessment for the risk of bias in included studies.

589x428mm (72 x 72 DPI)

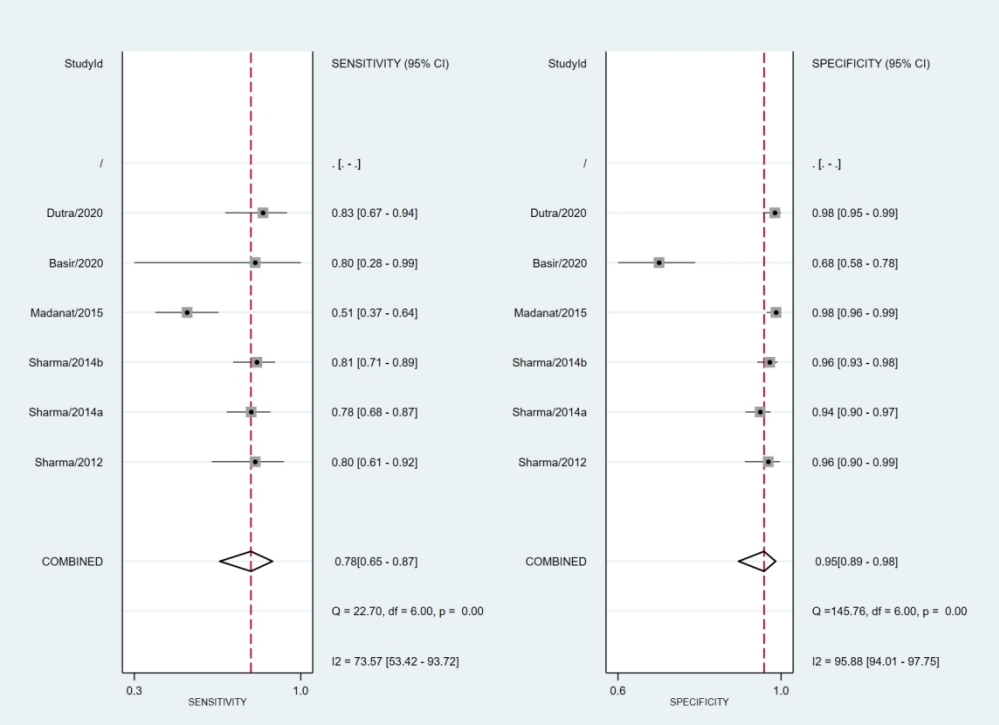

Figure4. Sensitivity and specificity of IPTT in the diagnosis of DPN.

589x428mm (72 x 72 DPI)

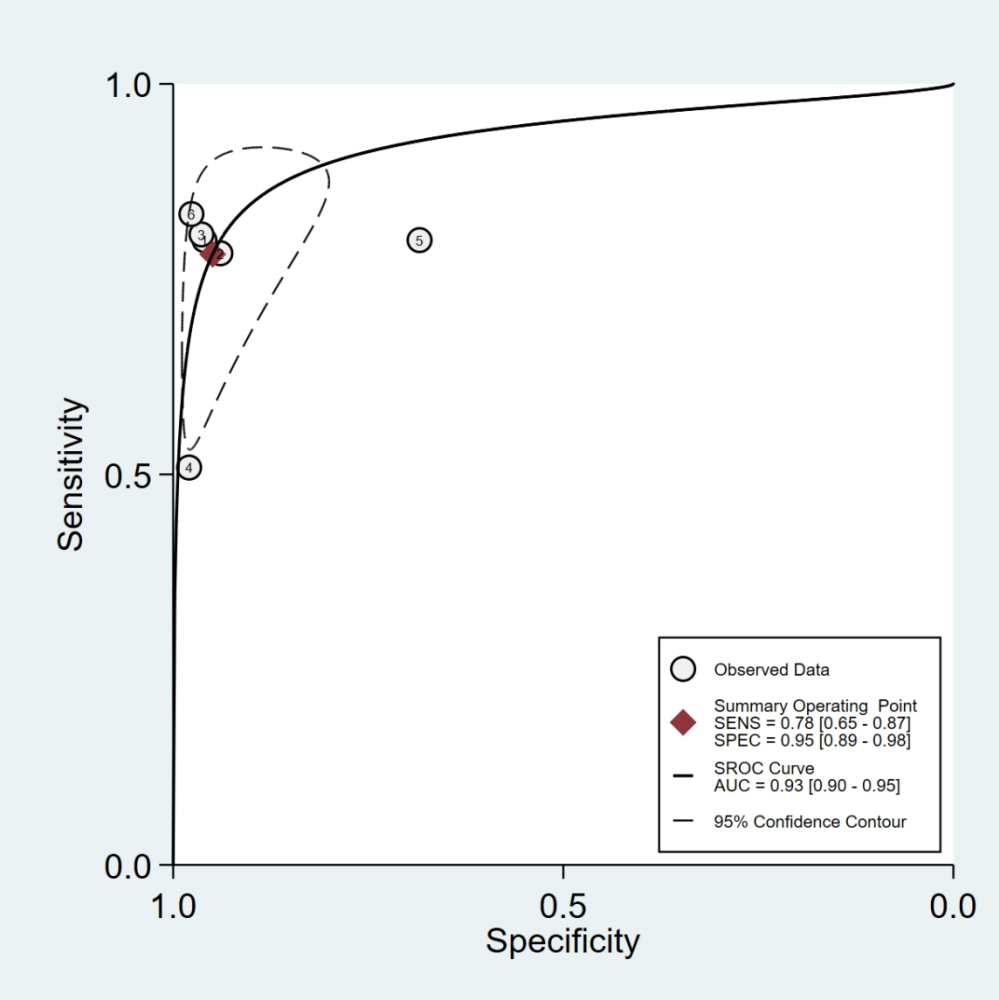

Figure 5. The SROC curve for quantitative analysis of IPTT in the diagnosis of DPN.

429x429mm (72 x 72 DPI)

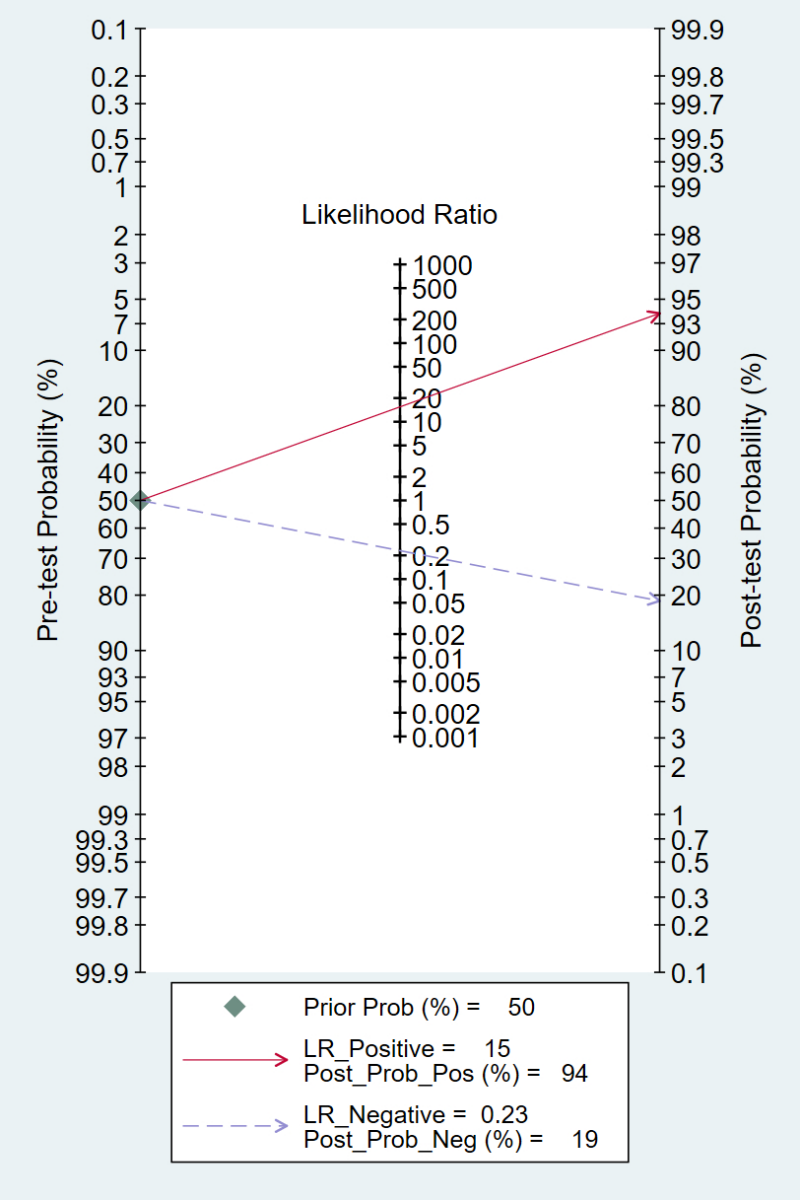

Figure 6. The Fagan for assessment of IPTT screening probability.

286x429mm (72 x 72 DPI)

Appendix S1

Search Strategy in PubMed, Embase, Cochrane Library, Web of Science, CNKI, CMB, Wanfang database.

PubMed Search Strategy

#1 Search: "Diabetes Mellitus"[Mesh] Sort by: Most Recent

#2 Search: ((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract])

#3 Search: "Diabetic Neuropathies"[Mesh] Sort by: Most Recent

#4 Search: ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR

(Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract])

#5 Search: "Diabetes Complications"[Mesh] Sort by: Most Recent

#6 Search:

#7 Search: "Diabetic Foot"[Mesh] Sort by: Most Recent

#8 Search: (((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])

#9 Search: ((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract])

#10 Search: (((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic

Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract]))

#11 Search: ((((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR

(Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])))) AND (((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract]))

Embase Search Strategy

#1 'diabetes mellitus'/exp

#2 'diabetes, type 2':ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'diabetes mellitus, type ii':ab,ti OR 'diabetes mellitus, type 1':ab,ti

#3 #1 OR #2

#4 'diabetic neuropathy'/exp

#5 'diabetic neuropathy':ab,ti OR 'neuropathies, diabetic':ab,ti OR 'neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathy':ab,ti OR 'autonomic neuropathies, diabetic':ab,ti OR 'autonomic neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathies':ab,ti OR 'neuropathies, diabetic autonomic':ab,ti OR 'neuropathy, diabetic autonomic':ab,ti OR 'symmetric diabetic proximal motor neuropathy':ab,ti OR 'asymmetric diabetic proximal motor neuropathy':ab,ti OR 'diabetic asymmetric polyneuropathy':ab,ti OR 'asymmetric polyneuropathies, diabetic':ab,ti OR 'asymmetric polyneuropathy, diabetic':ab,ti OR 'diabetic asymmetric polyneuropathies':ab,ti OR 'polyneuropathies, diabetic asymmetric':ab,ti OR 'polyneuropathy, diabetic asymmetric':ab,ti OR 'diabetic mononeuropathy':ab,ti OR 'diabetic mononeuropathies':ab,ti OR 'mononeuropathies, diabetic':ab,ti OR 'mononeuropathy, diabetic':ab,ti OR 'diabetic mononeuropathy simplex':ab,ti OR 'diabetic mononeuropathy simplices':ab,ti OR 'mononeuropathy simplex, diabetic':ab,ti OR 'mononeuropathy simplices, diabetic':ab,ti OR 'simplex, diabetic mononeuropathy':ab,ti OR 'simplices, diabetic mononeuropathy':ab,ti OR 'diabetic polyneuropathy':ab,ti OR 'diabetic polyneuropathies':ab,ti OR 'polyneuropathies, diabetic':ab,ti OR 'polyneuropathy, diabetic':ab,ti

#6 #4 OR #5

#7 'diabetic complication'/exp

#8 'diabetes complication':ab,ti OR 'diabetes-related complications':ab,ti OR 'diabetes related complications':ab,ti OR 'diabetes-related complication':ab,ti OR 'diabetic complications':ab,ti OR 'diabetic complication':ab,ti OR 'complications of diabetes mellitus':ab,ti OR 'diabetes mellitus complication':ab,ti OR 'diabetes mellitus complications':ab,ti

#9 #7 OR #8

#10 'diabetic foot'/exp

#11 'diabetic foot':ab,ti OR 'diabetic feet':ab,ti OR 'feet, diabetic':ab,ti OR 'foot ulcer,

diabetic':ab,ti OR 'foot ulcer':ab,ti

#12 #10 OR #11

#13 #3 OR #6 OR #9 OR #12

#14 'ipswich touch test':ab,ti OR 'touch test':ab,ti OR 'iptt':ab,ti

#15 #13 AND #14

Cochrane Library Search Strategy

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 31055

#2 (Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR (Diabetes Mellitus, Type 1)

#3 MeSH descriptor: [Diabetic Neuropathies] explode all trees

#4 (Diabetic Neuropathy):ti,ab,kw OR (Neuropathies, Diabetic):ti,ab,kw OR (Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathy):ti,ab,kw OR (Autonomic Neuropathies, Diabetic):ti,ab,kw OR (Autonomic Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathies):ti,ab,kw OR (Neuropathies, Diabetic Autonomic):ti,ab,kw OR (Neuropathy, Diabetic Autonomic):ti,ab,kw OR (Symmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Asymmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathy):ti,ab,kw OR (Asymmetric Polyneuropathies, Diabetic):ti,ab,kw OR (Asymmetric Polyneuropathy, Diabetic):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic Asymmetric):ti,ab,kw OR (Polyneuropathy, Diabetic Asymmetric):ti,ab,kw OR (Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Mononeuropathies):ti,ab,kw OR (Mononeuropathies, Diabetic):ti,ab,kw OR (Mononeuropathy, Diabetic):ti,ab,kw OR (Diabetic Mononeuropathy Simplex):ti,ab,kw OR (Diabetic Mononeuropathy Simplices):ti,ab,kw OR (Mononeuropathy Simplex, Diabetic):ti,ab,kw OR (Mononeuropathy Simplices, Diabetic):ti,ab,kw OR (Simplex, Diabetic Mononeuropathy):ti,ab,kw OR

(Simplices, Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Polyneuropathy):ti,ab,kw OR (Diabetic Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic):ti,ab,kw OR (Polyneuropathy, Diabetic):ti,ab,kw 3653

#5 MeSH descriptor: [Diabetes Complications] explode all trees

#6 (Diabetes-Related Complications):ti,ab,kw OR (Diabetes Related Complications):ti,ab,kw OR (Diabetes-Related Complication):ti,ab,kw OR (Diabetic Complications):ti,ab,kw OR (Diabetic Complication):ti,ab,kw OR (Complications of Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus Complication):ti,ab,kw OR (Diabetes Mellitus Complications)

#7 MeSH descriptor: [Diabetic Foot] explode all trees

#8 (Diabetic Feet):ti,ab,kw OR (Feet, Diabetic):ti,ab,kw OR (Foot Ulcer, Diabetic)

#9 (ipswich touch test):ti,ab,kw OR (touch test):ti,ab,kw OR (IPTT)

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#11 #9 AND #10

Web of Science Search Strategy

#1 TS=(Diabetes Mellitus or Diabetes or Diabetes, Type 2 or Type 2 Diabetes Mellitus or Diabetes Mellitus, Type II or Diabetes Mellitus, Type 1)

#2 TS=(Diabetic Neuropathies or Diabetic Neuropathy or Neuropathies, Diabetic or Neuropathy, Diabetic or Diabetic Autonomic Neuropathy or Autonomic Neuropathies, Diabetic or Autonomic Neuropathy, Diabetic or Diabetic Autonomic Neuropathies or Neuropathies, Diabetic Autonomic or Neuropathy, Diabetic Autonomic or Symmetric Diabetic Proximal Motor Neuropathy or Asymmetric Diabetic Proximal Motor Neuropathy or Diabetic Asymmetric Polyneuropathy or Asymmetric Polyneuropathies, Diabetic or Asymmetric Polyneuropathy, Diabetic or Diabetic Asymmetric Polyneuropathies or

Polyneuropathies, Diabetic Asymmetric or Polyneuropathy, Diabetic Asymmetric or Diabetic Mononeuropathy or Diabetic Mononeuropathies or Mononeuropathies, Diabetic or Mononeuropathy, Diabetic or Diabetic Mononeuropathy Simplex or Diabetic Mononeuropathy Simplices or Mononeuropathy Simplex, Diabetic or Mononeuropathy Simplices, Diabetic or Simplex, Diabetic Mononeuropathy or Simplices, Diabetic Mononeuropathy or Diabetic Polyneuropathy or Diabetic Polyneuropathies or Polyneuropathies, Diabetic or Polyneuropathy, Diabetic)

#3 TS=(Diabetes Complications or Diabetes Complication or Diabetes-Related Complications or Diabetes Related Complications or Diabetes-Related Complication or Diabetic Complications or Diabetic Complication or Complications of Diabetes Mellitus or Diabetes Mellitus Complication or Diabetes Mellitus Complications)

#4 TS=(Diabetic Foot or Foot, Diabetic or Diabetic Feet or Feet, Diabetic or Foot Ulcer, Diabetic)

#5 #4 OR #3 OR #2 OR #1

#6 TS=(ipswich touch test or touch test or IPTT)

#7 #6 AND #5

China National Knowledge Infrastructure (CNKI) Search Strategy

检索式 A: (((主题=糖尿病 或者 题名=糖尿病 或者 v_subject=中英文扩展(糖尿病) 或者 title=中英文扩展(糖尿病)) 或者 (主题=糖尿病足 或者 题名=糖尿病足 或者 v_subject=中英文扩展(糖尿病足) 或者 title=中英文扩展(糖尿病足))) 或者 ((主题=糖尿病周围神经病变 或者 题名=糖尿病周围神经病变 或者 v_subject=中英文扩展(糖尿病周围神经病变) 或者 title=中英文扩展(糖尿病周围神经病变)) 或者 (主题=糖尿病并发症 或者 题名=糖尿病并发症 或者 v_subject=中英文扩展(糖尿病并发症) 或者 title=中英文扩展(糖尿病并发症)))) 并且 (((((主题=中英文扩展(touch test) 或者 题名=中英文扩展(touch test) 或者 v_subject=touch test 或者 title=touch test) 或者 (主题=中英文扩展(Ipswich Touch Test) 或者 题名=中英文扩展(Ipswich Touch Test) 或者

v_subject=Ipswich Touch Test 或者 title=Ipswich Touch Test)) 或者 ((主题=伊普斯维奇触摸测试 或者 题名=伊普斯维奇触摸测试 或者 v_subject=中英文扩展(伊普斯维奇触摸测试) 或者 title=中英文扩展(伊普斯维奇触摸测试)) 或者 (主题=中英文扩展(IPTT) 或者 题名=中英文扩展(IPTT) 或者 v_subject=IPTT 或者 title=IPTT))) 或者 ((关键词=轻触 或者 keyword=中英文扩展(轻触)) 或者 (关键词=轻触测试 或者 keyword=中英文扩展(轻触测试)))) 或者 ((题名=触摸 或者 Title=中英文扩展(触摸)) 或者 (题名=触摸测试 或者 Title=中英文扩展(触摸测试)))) (模糊匹配)

Wan Fang Database Search Strategy

主题:((糖尿病)+主题:(糖尿病足)+主题:(糖尿病周围神经病变)+全部:(糖尿病并发症))*主题:((touch test)+主题:(IPTT)+主题:(Ipswich Touch Test)+全部:(伊普斯维奇触摸测试))

China Biology Medicine disc (CBM) Search Strategy

#1 "糖尿病"[不加权:扩展]

#2 "糖尿病足"[常用字段:智能]

#3 "糖尿病神经病变"[常用字段:智能]

#4 "糖尿病并发症"[常用字段:智能]

#5 (#4) OR (#3) OR (#2) OR (#1)

#6 "touch"[常用字段:智能] AND "test"[常用字段:智能]

#7 "IPTT"[常用字段:智能]

#8 "Ipswich"[常用字段:智能] AND "Touch"[常用字段:智能] AND "Test"[常用字段:智能]

#9 "伊普斯维奇触摸测试"[常用字段:智能]

#10 "轻触"[常用字段:智能]

#11 "轻触测试"[常用字段:智能]

#12 "触摸"[常用字段:智能]

#13 "触摸测试"[常用字段:智能]

#14 (#13) OR (#12) OR (#11) OR (#10) OR (#9) OR (#8) OR (#7) OR (#6)

#15 (#14) AND (#5)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: Diabetic peripheral neuropathy (DPN) is one of the most important risk factors of diabetic foot ulcers (DFU), and early screening and treatment of DPN are crucial. The Ipswich Touch Test (IPTT) is a new method for screening for DPN and, compared with traditional methods, is more simple to operate and requires no equipment. However, the screening accuracy of IPTT in DPN patients has not been well characterized. We aim to conduct a systematic review and meta-analysis to characterize the sensitivity and specificity of IPTT compared to traditional methods and to understand the potential screening value of IPTT.

Design： Systematic review and meta-analysis.

Data sources： PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Database (CBM) up to April 16, 2020.

Methods: Stata version 15.1 software was used for analysis, and the screening value of IPTT in DPN was described using 10g-MF, NDS, Pin prick, 128Hz tuning fork, and ankle reflex as reference standards. Sensitivity, specificity, and other measures of accuracy of IPTT for screening DPN were pooled based on a quality effects model. The protocol was registered with PROSPERO (42020168420).

Results: Of the 441 records retrieved, seven studies were evaluated for the screening value of IPTT. Five studies with 10g-MF as the reference standard were included in the meta-analysis, and the pooled sensitivity and specificity were 0.78 (95 % CI 0.65–0.87) and 0.95(95 % CI 0.89–0.98), respectively, and AUC was 0.93. Compared with VPT, IPTT showed a sensitivity between 0.76 and 1, and a specificity between 0.90 and 0.97. Compared with NDS, IPTT showed a sensitivity between 0.53 and 1, and a specificity between 0.90 and 0.97. Compared with Pin prick, IPTT showed a

sensitivity and specificity of 0.8 and 0.88, respectively. Compared with 128Hz tuning fork, IPTT showed a sensitivity and specificity of 0.4 and 0.27, respectively. Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97.

Conclusions: IPTT has a high degree of agreement in DPN screening with commonly used screening tool for DPN. It can be used clinically, especially in remote areas and in primary medical institutions, and by self-monitoring patients. More high-quality studies are needed to assess and promote more effective screening practices.

Prospero: Registration Number is CRD (42020168420)

Strengths and limitations of this study

- This is the first meta-analysis to explore the potential screening value of IPTT in DPN.
- A quality effects model was used to achieve optimal error estimation in the data analysis.
- Based on the existing evidence, the value of IPTT in DPN screening is summarized, and it provides evidence for medical staff to use IPTT for DPN screening.
- By facilitating the identification of patients at risk for foot ulceration, we can effectively prevent the occurrence of DFU, and reduce the social and economic burden of this disease.
- Although we have systematically and comprehensively studied the current evidence of IPTT screening in DPN, still the original studies are very limited, and the existing conclusions are only based on these 7 original studies. Therefore, caution should be taken when popularizing them.

Keywords: Ipswich Touch Test, Diabetic peripheral neuropathy, Meta-analysis

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common long-term complication and the most important risk factor for the occurrence of diabetic foot ulcers (DFU).[1-4] DPN affects up to 50% of people with diabetes,[5,6] with chronic painful neuropathy affecting up to 26%.[7] In the early stage of DPN, the

symptoms lack specificity, and about half of patients with diabetes cannot recognize the injury to the lower extremities.[8,9] Once the patient has symptoms such as limb numbness and pain, it signals that pathological changes have occurred in the peripheral nerves and have advanced into the irreversible stage. If not treated promptly, serious tissue damage, such as foot ulcers, amputation, and even death, may occur.[10,11] Studies have shown that early screening and detection of peripheral neuropathy can not only slow down the DPN process, but also effectively prevent DFU.[12] Therefore, early screening and treatment of DPN is very important.

At present, the screening value of 10g monofilament (10g-MF), Vibration perception threshold (VPT), and 128Hz tuning fork in DPN has been widely recognized.[13] Compared with VPT and 128Hz tuning forks, 10g-MF is the most widely used screening tool because it is more simple, objective, and easy to carry, although it requires a calibration facility to confirm that the vertical pressure of the monofilament used when bending is 10g.[14-16] Commercially available 10g-MF devices exhibit significant variability within and between devices of different manufacturers and their actual bending force varies widely from their designated 10g value. When used they have a short service life where the instrument is within 10% of their initial bending force which is not usually the stated 10g of force.[17,18] Meanwhile, medical personnel are required to be trained before using the device, and screening is limited to hospitals or clinics. For clinics and communities in remote areas, medical personnel may lack the device or the training to screen patients for DPN, resulting in a missed opportunity for patients to receive the best treatment. In recent years, Dr. Rayman proposed the Ipswich Touch Test (IPTT), which only requires the physician's index finger. During this test, the patient is required to close their eyes while the physician lightly rests their finger on each of the patient's first, third, and fifth toes for 1 to 2 seconds. Patients are instructed to respond with a "yes" when they feel the physician's touch. Compared with the current methods, IPTT requires no equipment, is more convenient and effective, and can be performed by doctors, nurses, and even family caregivers after training.[19] IPTT can be applied to inpatients, outpatients, community patients, self-monitoring patients at home, and to areas lacking more advanced equipment.[20,21] Currently, IPTT has been applied in the United Kingdom, Spain, Brazil, and Saudi Arabia,[19,22-26] and was approved by the American Diabetes Association in 2015.[20] The 2019

guidelines of the International Working Group on the Diabetic Foot also suggest that IPTT should be used for DPN screening in patients with diabetes in the absence of 10g-MF.[27] Although these studies have achieved satisfactory results, they have not been widely promoted and applied globally. Previous studies have reported differences in the results of the screening value of DPN. However, neither a meta-analysis nor a systematic review has been conducted on the screening value of IPTT.

In this study, we aimed to conduct a comprehensive and systematic literature review to systematically evaluate the potential screening value of IPTT in DPN, and provide evidence and guidance for the clinical application value of IPTT.

METHODS

The Joanna Briggs Institute (JBI) protocol[28] has been registered with PROSPERO, the International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination (Registration Number is CRD (42020168420). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[29].

Data Sources and Searches

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Biomedical Literature Database (CBM) for reports published before April 16, 2020. For included studies with insufficient data, we emailed the authors to ask if they would provide data for our study. With this strategy, we combined search terms for applied technique (Ipswich touch test, touch test, IPTT) and disease (Diabetic peripheral neuropathy, diabetic foot, diabetic foot ulcer, Diabetes Mellitus, diabetic complications). The study design and published language were not limited. In addition, we conducted a manual search, including searching through conference papers and gray literature, and the references of all included studies were examined. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database. A detailed search strategy is provided in “Supplementary files 1”. All analyses were based on previously published studies; thus, no ethical approval and patient consent were required.

Inclusion and Exclusion Criteria

Previously published studies were included in this meta-analysis if: (1) the study was designed as a diagnostic test and systematic reviews; (2) all the research subjects were patients with diabetes, and; (3) IPTT was included as an index test. Studies were excluded from the meta-analysis if the studies had incomplete data sets or were other than original reports (commentaries/reviews). The age, sex, region, and race of the subjects were not restricted. The published language was not limited.

Data Extraction and Quality Assessment

We imported initial search records from databases into NoteExpress V3.2.0.7535 literature management software. Two reviewers independently screened titles and abstracts of all the included literature, following the inclusion and exclusion criteria. After screening the abstract, the full text was read in detail. Any discrepancies were resolved by discussion. The following information was extracted from the eligible studies: study characteristics (author, publication year, study period, country, reference standard, setting, operators), participant characteristics (sample number, range), and outcome indicators (sensitivity, specificity, true positive number (TP), false positive number (FP), false negative number (FN), true negative number (TN)). Missing data were supplemented by contacting authors wherever possible.

The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS), it is a methodological quality assessment scale, and includes 14 items[30]. Quality items were weighted equally with 1 point awarded for each of the 14 items. The quality score was then calculated by summing the points awarded for each question (maximum sum 14). This score was then normalized by dividing the sum by the highest score of the listed studies, thereby ranking the studies from 1 down to a minimum of 0.[31] Data extraction and quality assessment was performed independently by two reviewers. Differences were reconciled through discussion until a consensus was reached on the item in question.

Data Synthesis

The sensitivity, specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and

corresponding 95% confidence intervals (95% CIs) were calculated using the TP, FP, FN, and TN values, which were extracted from each study prior to data pooling. The likelihood ratio is an independent indicator to assess authenticity, which can simultaneously reflect sensitivity and specificity. When the PLR is >10 or the NLR is <0.1, the probability of diagnosing or excluding a certain disease increases significantly. The likelihood ratio is more clinically significant than summary receiver operating characteristic curve (SROC) and diagnostic odds ratio (DOR) value.[32] The DOR with 95% CI was also calculated. For each summary statistic, a 95% confidence interval was computed. The quality effects model in meta-analysis was used to estimate variance between studies by using STATA, version15.1 (Stata Corp, College Station, TX).[33,34] Relevant studies have proven that this model is superior to the traditional random effects model and fixed effects model.35-37 The quality scores were used to redistribute inverse variance weights based on study deficiencies via the quality effects model.[38,39]

In addition, Fagan nomograms were generated to evaluate the clinical utility of the two screening methods. Heterogeneity among the reports was assessed by the χ^2 test (Cochran Q test) and the I^2 statistic, where $p \leq 0.05$ or an $I^2 \geq 50\%$ indicated the existence of significant heterogeneity.[40] If there was significant heterogeneity ($p \leqslant 0.05$ or $I^2 \geqslant 50\%$), sensitivity analysis was conducted to assess stability between studies.41 Publication bias was assessed with Doi plots and the Luis Furuya-Kanamori (LFK) index quantified the asymmetry in the Doi plots. The Doi plot uses a rank-based measure (Z score) of precision (instead of the standard error) and plots it against the effect size, and the LFK index quantifies the extent of Doi plot asymmetry by averaging half of the sum of the Z score plus the normalized effect size across the meta-analysis. The closer the value of the LFK index is to zero, the more symmetrical the Doi plot.[42] LFK index values outside the interval of -1 and +1 are deemed consistent with asymmetry.[42]

Patient and public involvement

Patients and the public were not involved in this research.

RESULTS

Study Selection

Our initial search resulted in a total of 441 records: 437 from database searching and four records from manual searches of references. After duplicates were removed, 242 records were identified, and 220 records were excluded as irrelevant. After reading the full-text articles, 7 studies met the inclusion criteria (Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.). Two studies were excluded for lacking necessary data for meta-analysis. Finally, five studies with 6 datasets were included in the final meta-analysis, involving a total of 1162 patients.[22-26]

Characteristics and Quality of the Included Studies

The characteristics of the included studies are presented in Table 1. The 7 studies included a total of 1,510 participants with diabetes and were published between 2011 and 2020.[19,22-27] 10g-MF, VPT, NDS, pin prick, tuning fork 128Hz, and ankle reflex were used as the reference standard to explore the accuracy of IPTT in DPN. The research setting included homes of patients, clinics, care centers, and outpatient centers, and the assessors included doctors, nurses, and family caregivers.

We assessed the methodological quality of the studies using QUADAS. The assessment results of the research methodological quality of each study are presented in Figures 2.[43]

Table 1. Basic characteristics of the included studies.

Study	Year	Country	n	Setting	Operators	Quality score(Qi)	Reference standard	TP	FP	FN	TN	Se(%)	Sp (%)
Sharma[22]	2012	UK	130	home	families	0.074	10g-MF	24	4	6	96	80.0	96.0
Sharma[23]	2014	UK	331	home	families	0.714	10g-MF	65	15	18	233	78.3	93.9
				clinic	doctors/ nurses	0.786	10g-MF	67	9	16	239	81.2	96.4
Amal Madanat[24]	2015	Saudi Arabia	351	care centers	doctors/ nurses	0.357	10g-MF	29	6	28	288	51.0	98.0
							VPT	48	24	9	270	85	92
							NDS	30	9	27	285	53	97
I.S, Basir[25]	2020	Spain	100	care centers	doctors/ nurses	0.429	10g- MF	4	30	1	65	80.0	68.0
							Pin prick	4	1	11	84	80.0	88.0
							Tuning fork 128Hz	2	3	69	26	40.0	27.0
							Ankle reflex	1	4	2	93	20.0	97.0
Dutra[26]	2020	Brasília	250	outpatient centre	doctors/ nurses	0.643	10g-MF	30	5	6	209	83.3	97.7
Rayman[19]	2011	UK	265	clinic	-	-	VPT	-	-	-	-	76.0	90.0
Bowling[27]	2012	UK	83	clinic	doctors/ nurses	-	VPT	-	-	-	-	100	96.6
							NDS	-	-	-	-	100	90.3

Se, Sensitivity; Sp, Specificity

Screening Accuracy

In the included studies, the researchers used a variety of different test methods as the standard to observe the sensitivity and specificity of IPTT for screening for DPN, such as 10g-MF, VPT, NDS, tuning fork 128Hz, and ankle reflex. The differences in the sensitivity and specificity of IPTT obtained by using different test methods as reference standards are presented. In general, when 10g-MF and VPT were used as reference standards, the sensitivity and specificity of IPTT were relatively high. For the 5 studies comprising 6 data pools that used 10g-MF as the reference standard, the sensitivity ranged from 51.0% - 83.3%, and the specificity ranged from 68.0 - 98.0%.[22-26] For the 3 studies that used VPT as a reference standard, the sensitivity ranged from 76.0 - 100.0%, and the specificity ranged from 90.0 - 96.6%. Using neuropathy disability scores (NDS) as the reference standard, the sensitivity of IPTT to be 0.53, and the specificity to be 0.97. Compared with the pin prick, the sensitivity and specificity of IPTT were 0.8 and 0.88, respectively.[24] Compared with 128Hz tuning fork, the sensitivity and specificity of IPTT were only 0.4 and 0.27, respectively.[25] Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97(Table 1).[25]

Meta-analysis Results Using 10g-MF as the Reference Standard

Screening Accuracy

In the literature we retrieved, there were a total of 5 studies with IPTT as the target test and 10g-MF as the reference standard.[22-26] Among these 5 studies, one study has two datasets because it was conducted in the patient's home and the clinic.[22] Therefore, six datasets were included to evaluate the overall effect of IPTT in the screening of DPN. [22-26] The combined sensitivity and specificity were 0.77 (95 % CI 0.69–0.84) and 0.96 (95 % CI 0.93–0.98), respectively. The results show I - squared is 40.5%. In addition, the DOR was 75.24(39.90-141.89). The SROC analysis for the studies yielded an overall weighted area under the curve of 0.90(0.86-0.92) (Figure 3; Supplementary Files 2).

Sensitivity Analysis and Fagan's analysis

After excluding each study, the difference between the combined effect and the value before exclusion was minor, suggesting the results of this study are stable (Supplementary Files 3). Fagan's analysis showed that the pre-test probability was 50%, the probability of a positive result for DPN detected by IPTT was 94%, and the probability of a negative result for DPN detected was 23%. Further, the positive likelihood ratio was 15, and the negative likelihood ratio was 0.23. The above results demonstrate that there is a good diagnostic value of IPTT for DPN (Figure 4).

Publication Bias

The LFK index was calculated to be -1.68, and the Doi plot and LFK index showed minor asymmetry, which means that there is a slight publication bias (Figure 5).

DISCUSSION

DPN is the most important risk factor for the occurrence of DFU and one of the more common chronic complications associated with diabetes. However, it is often ignored. Once the patient develops DPN, it is likely to cause diabetic foot ulcers, gangrene, and even amputation, and many patients experience numbness and tingling in their limbs. Early identification of DPN can greatly reduce the burden of chronic diseases on society. In this study, we systematically reviewed the relevant literature on the identification of DPN by IPTT. A total of 7 studies were included, involving 1,510 participants with diabetes to explore the value of IPTT screening. Previous studies have disputed the diagnostic value of IPTT, mainly due to the use of different test methods, such as VPT, NDS, pinprick, tuning fork 128Hz, and ankle reflex, as the reference standard.[33] Compared with NDS, acupuncture, 128Hz tuning fork, and ankle reflex, IPTT has higher screening accuracy when 10g-MF and VPT were used as the reference standard.[10,19,20] Basir et al. observed that when 128Hz tuning fork was used as a reference standard, the sensitivity and specificity of IPTT were only 40% and 27%, respectively. This may be since the predictive level of a tuning fork is less than that of the monofilament. However, Miller et al observed that combining a tuning fork with monofilament would result in a more effective evaluation.[21] Regarding the quality of the current studies, some studies lacked rigor in study design, such as the interval between target tests and unclear reference standard tests, and most studies failed to describe the reference methods in detail.

The overall quality of the included studies was rated as low to medium quality.

Compared with 10g-MF, the results of the meta-analysis found the combined sensitivity and specificity of IPTT to be 0.77(95％CI 0.69-0.84) and 0.96(95％CI 0.93-0.98), respectively, and AUC to be 0.90(95％CI 0.86-0.92). The results indicated that IPTT had a moderate to high level of sensitivity and a high level of specificity for screening DPN. In our analysis, a DOR equal to 1 indicated that a test was unable to distinguish between patients with or without the disease. Our study yielded a DOR value of 75.24(95％CI 39.90-141.89), indicating that NLR had a certain accuracy in the diagnosis of patients with DPN. We also found that when VPT is used as reference standards, IPTT has higher sensitivity and specificity. At present, 10g-MF and VPT are the most widely used clinical screening methods for DPN. Basir et al. explored the accuracy of using IPTT in detecting neuropathy in patients with small fiber and large fiber neuropathy, the result shows that there is no difference between the IPTT against the golden standard small fiber neuropathy large fiber neuropathy, and they concluded that the IPTT can be used an alternative assessment.[25] Therefore, the current evidence shows that IPTT has a high screening value for DPN and can be used for preliminary screening of DPN in areas lacking equipment.

We also drew Fagan's plot, the results show that IPTT has a certain potential screening value of IPTT in DPN. Previous studies have shown that the prevalence of DPN is 50%, when the pre-test probability of 50% through the likelihood ratio of 15, the line intersects with the post-test probability of about 94%, this means that the probability of the diabetic patient with DPN will increase from 50% to 94% when he or she has had a positive result for Test IPTT, at this time, electromyography and nerve conduction velocity tests may be recommended by the clinician to determine whether the patient has DPN; Joining the pre-test probability of 50% to the likelihood ratio of 0.23 on the Fagan's nomogram, we read a post-test probability of about 19%, this means that after a negative test, a person in this population's chance of having DPN reduces from 50% to 19%, this means that if the patient tests negative, her chance of having DPN would decrease from 50% to a very low risk of

19%. This may make the doctor decide not to recommend electromyography and nerve conduction velocity tests (Figure 4).

Heterogeneity is an important factor of this meta-analysis. In this study, we chose the quality effects model because it has been proven to be significantly better than the traditional random effects model and fixed effects model at effectively avoiding the problem of high heterogeneity caused by statistical analysis. When 10g-MF was used as the reference standard, the I^2 was only 40.5%, indicating that there was good consistency among the five studies included in the meta-analysis. In addition, the existence of heterogeneity may be related to some other factors, such as differences in research methodology, operators, or other factors. Due to the limited number of included studies, we did not analyze the heterogeneity through subgroup analysis in this study. In terms of methodology, although we have systematically and comprehensively studied the current evidence of IPTT screening in DPN, still the original studies are very limited, and the existing conclusions are only based on these 7 original studies. Therefore, caution should be taken when popularizing them. About using other test methods as the reference standard (except 10g-MF), we only described the relevant indicators as there were too few related studies to merge data, this was also one of the limitations of our study.

Studies have shown that routine foot examinations and rapid risk stratification are often difficult to implement in busy primary care institutions. Additionally, the lack of awareness of standardized testing for DPN amongst healthcare professionals is a concern, which may be due to a shortage of material and personnel resources in primary care institutions. This is concerning because identifying foot neuropathy and the patients at risk for ulceration has been shown to prevent the incidence of foot ulcers.[44-46] IPTT is a new method for screening DPN that does not require any tools and can be carried out after minimal training. It is not affected by time, venue, or its operators.[20] The advancement of IPTT is of great significance for the early screening of DPN to impede the progression of diabetic foot ulcers, as it can be used to quickly and reliably screen and manage patients at high risk for ulceration, especially in remote areas or places lacking screening tools.[47,48] Kerry et al. reported that in the first year IPTT was introduced as a screening tool, the relative risk reduction (RRR) of DFU was 64%, and in the second year, the RRR was 70%, thereby reducing

hospital-acquired foot ulcers in patients with diabetes by two-thirds and negating the excess risk associated with diabetes.[20,49-51] Meanwhile, it can effectively improve patients' disease-related knowledge, which plays a positive role in promoting the self-management of patients and their families. At the same time, IPTT has a predictive effect on diabetic foot ulcers and reduces delays in patient visits.[21] However, more thorough studies are needed for verification.

Most of the literature on IPTT is focused on screening tests and some commentary-type studies, and the number of studies is small. These studies were carried out in the United Kingdom, Spain, Brazil, and Saudi Arabia, and although they achieved satisfactory results, have not been carried out globally. However, it has not been applied in developing countries such as China. China is a country with a large population and a relatively small number of medical personnel, especially in some remote areas where the medical allocation is in short supply. In these areas, the application and promotion of IPTT can effectively alleviate the allocation of medical resources and play an important role in the management of patients with diabetes. IPTT has also recently been approved for use in some countries.[21,24-26] However, Kempegowda et al. reported that 88.4% of physicians are not familiar with IPTT. Therefore, we suggest that IPTT be further promoted amongst physicians and medical staff, especially in remote areas and areas lacking screening tools.[36] Future large-scale, high-quality, and multi-center studies on populations of different ethnicities will verify the potential applicability of IPTT alone or in combination with other DPN screening methods.

CONCLUSIONS

In summary, IPTT has a high degree of agreement in DPN screening with commonly used screening tool for DPN, it can be used clinically, especially in remote areas and primary medical institutions, and self-monitoring patients. This is also the first meta-analysis of the accuracy of IPTT identification of DPN, and a systematic quantitative evaluation of its screening value, which can provide evidence for the clinical application of IPTT in the future. However, due to a limited number of studies of low or medium quality from limited geographical areas, more high-quality studies are needed to promote more effective screening practices.

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Author contributions

ZN conducted the database search, screened and extracted data for the meta-analysis, prepared extracted data for the procedures, and had primary responsibility in writing this article. LXY, ZJ and ZF performed statistical analysis and contributed to article screening, data collection and extraction. XJC, ZQH, and LJH contributed to the discussion and editing. XJC and CJR critically revised the draft manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Competing interests

The authors state that they have no conflict of interest.

Patient consent for publication

Not required. All analyses were conducted based on previously published studies. Accordingly, there was no patient or public involvement in this study. Ethical approval is not needed as it is a systematic review of published literatures.

Data availability statement

Data are available in a public, open access repository. There are no data in this work. Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. No data are available. All data relevant to the study are included in the article or uploaded as supplementary information.

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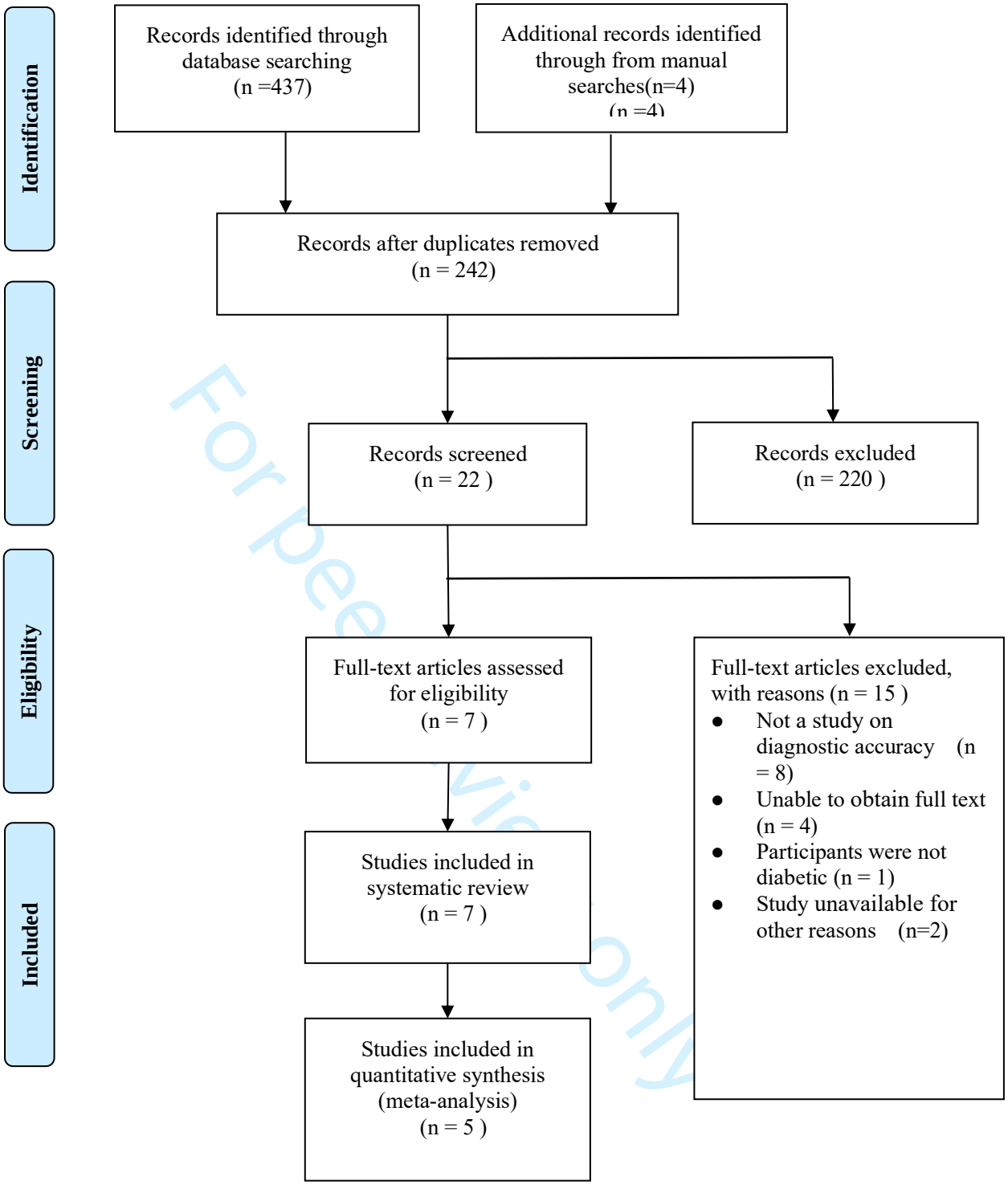


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

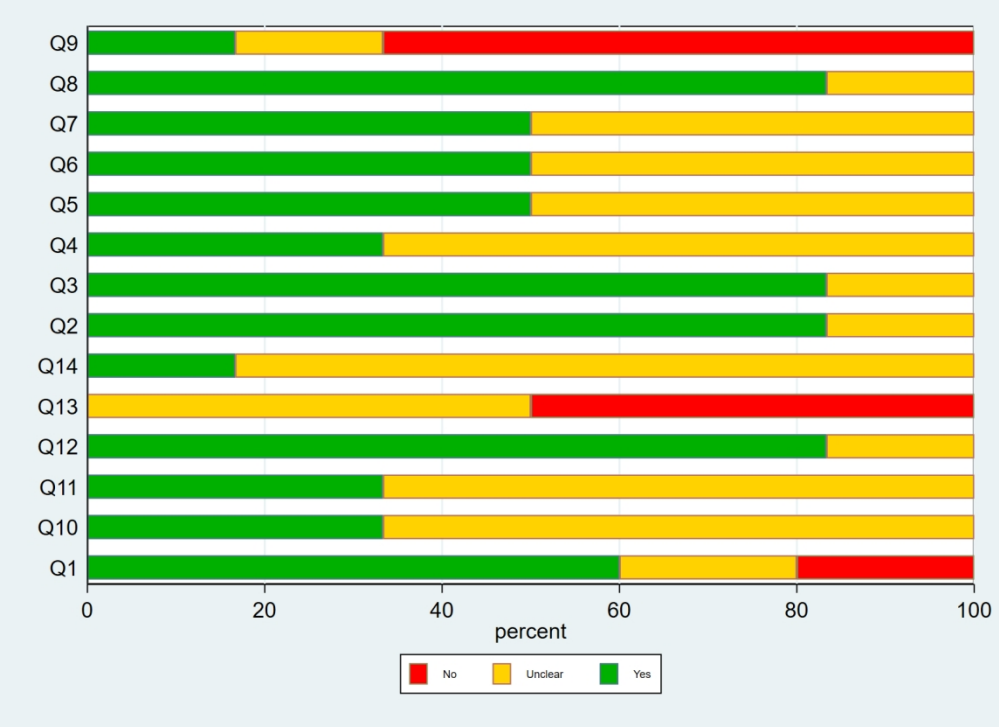


Figure 2 quality assessment of the included studies

589x428mm (72 x 72 DPI)

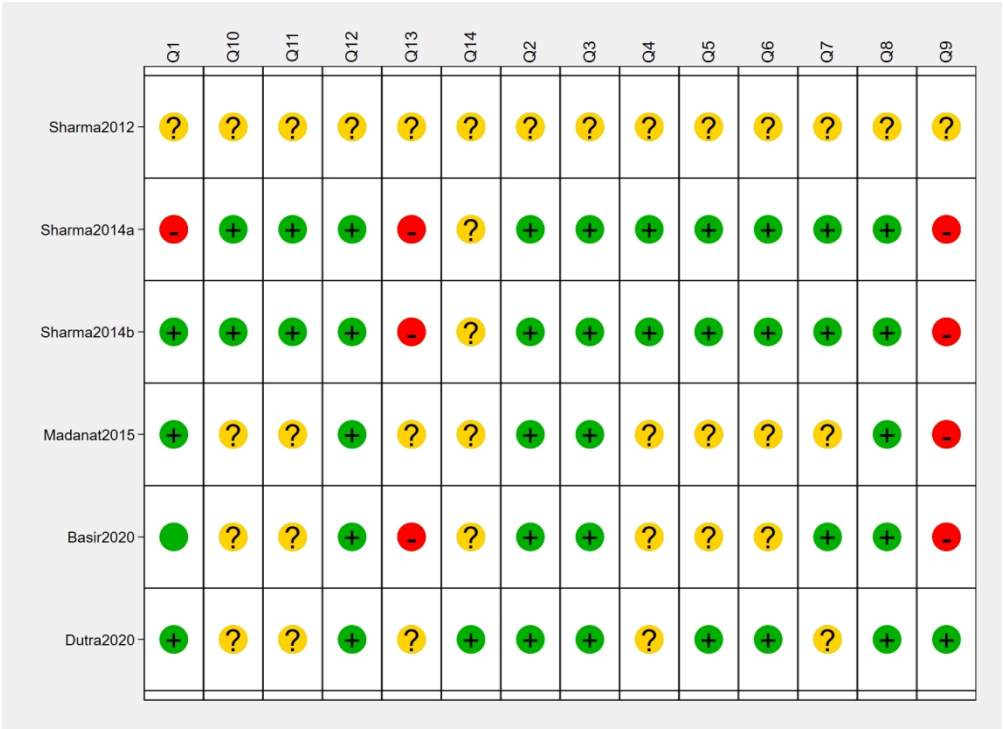


Figure 2. quality assessment of the included studies

589x428mm (72 x 72 DPI)

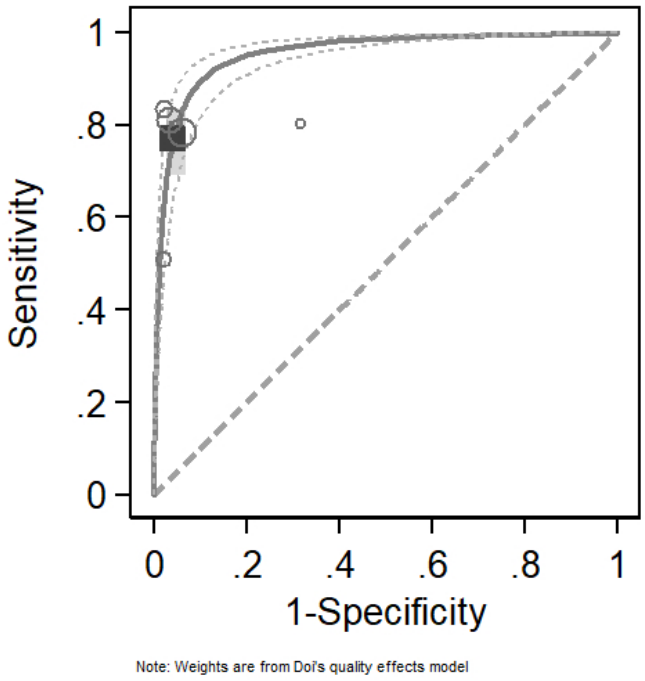


Figure 3. Sensitivity and specificity of IPTT in the diagnosis of DPN

255x185mm (72 x 72 DPI)

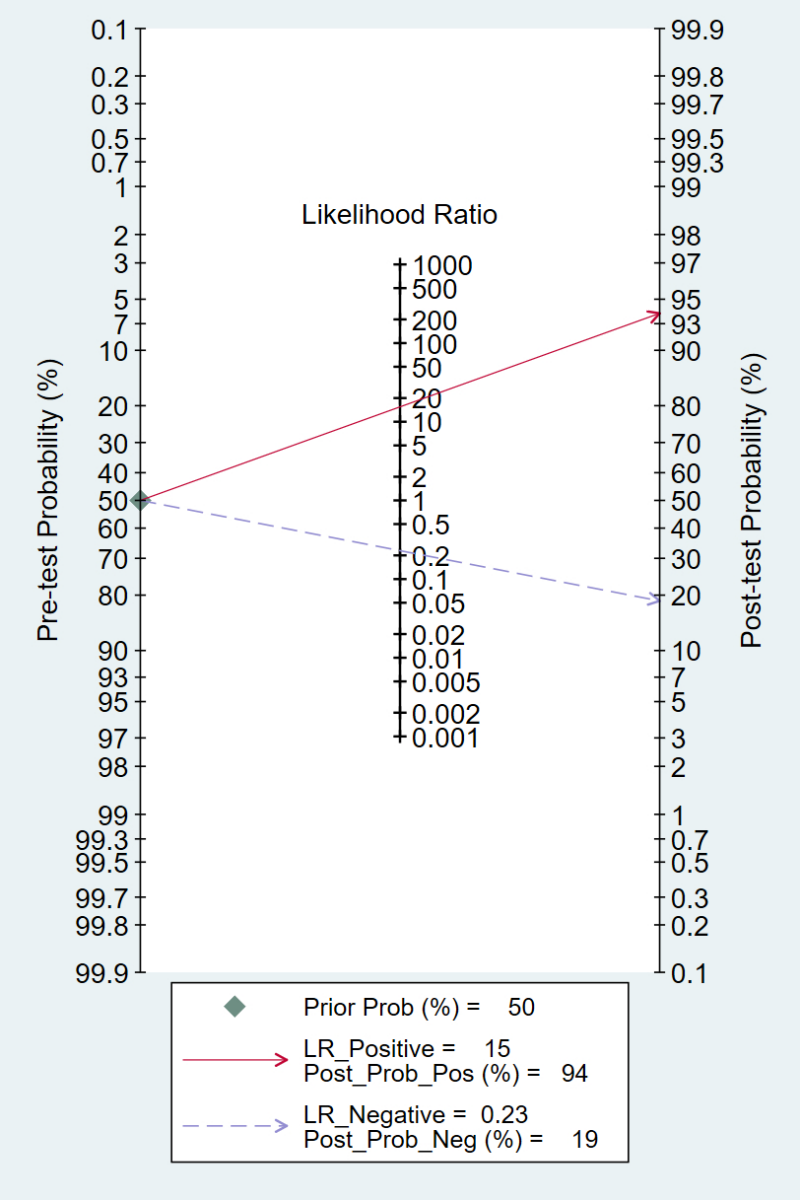


Figure 4. The Fagan for assessment of IPTT screening probability.

286x429mm (72 x 72 DPI)

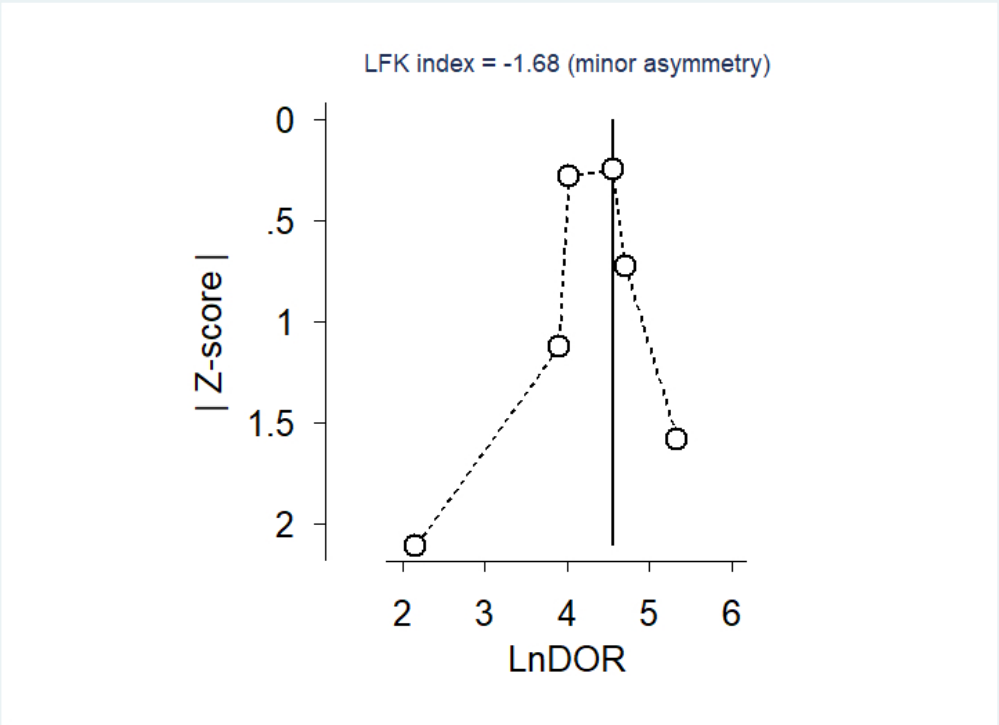


Figure 5. Doi plot and LFK index.

255x185mm (72 x 72 DPI)

Appendix S1

Search Strategy in PubMed, Embase, Cochrane Library, Web of Science, CNKI, CMB, Wanfang database.

PubMed Search Strategy

#1 Search: "Diabetes Mellitus"[Mesh] Sort by: Most Recent

#2 Search: ((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract])

#3 Search: "Diabetic Neuropathies"[Mesh] Sort by: Most Recent

#4 Search: ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR

(Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract])

#5 Search: "Diabetes Complications"[Mesh] Sort by: Most Recent

#6 Search:

#7 Search: "Diabetic Foot"[Mesh] Sort by: Most Recent

#8 Search: (((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])

#9 Search: ((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract])

#10 Search: (((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic

Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract]))

#11 Search: ((((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR

(Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])))) AND (((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract]))

Embase Search Strategy

#1 'diabetes mellitus'/exp

#2 'diabetes, type 2':ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'diabetes mellitus, type ii':ab,ti OR 'diabetes mellitus, type 1':ab,ti

#3 #1 OR #2

#4 'diabetic neuropathy'/exp

#5 'diabetic neuropathy':ab,ti OR 'neuropathies, diabetic':ab,ti OR 'neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathy':ab,ti OR 'autonomic neuropathies, diabetic':ab,ti OR 'autonomic neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathies':ab,ti OR 'neuropathies, diabetic autonomic':ab,ti OR 'neuropathy, diabetic autonomic':ab,ti OR 'symmetric diabetic proximal motor neuropathy':ab,ti OR 'asymmetric diabetic proximal motor neuropathy':ab,ti OR 'diabetic asymmetric polyneuropathy':ab,ti OR 'asymmetric polyneuropathies, diabetic':ab,ti OR 'asymmetric polyneuropathy, diabetic':ab,ti OR 'diabetic asymmetric polyneuropathies':ab,ti OR 'polyneuropathies, diabetic asymmetric':ab,ti OR 'polyneuropathy, diabetic asymmetric':ab,ti OR 'diabetic mononeuropathy':ab,ti OR 'diabetic mononeuropathies':ab,ti OR 'mononeuropathies, diabetic':ab,ti OR 'mononeuropathy, diabetic':ab,ti OR 'diabetic mononeuropathy simplex':ab,ti OR 'diabetic mononeuropathy simplices':ab,ti OR 'mononeuropathy simplex, diabetic':ab,ti OR 'mononeuropathy simplices, diabetic':ab,ti OR 'simplex, diabetic mononeuropathy':ab,ti OR 'simplices, diabetic mononeuropathy':ab,ti OR 'diabetic polyneuropathy':ab,ti OR 'diabetic polyneuropathies':ab,ti OR 'polyneuropathies, diabetic':ab,ti OR 'polyneuropathy, diabetic':ab,ti

#6 #4 OR #5

#7 'diabetic complication'/exp

#8 'diabetes complication':ab,ti OR 'diabetes-related complications':ab,ti OR 'diabetes related complications':ab,ti OR 'diabetes-related complication':ab,ti OR 'diabetic complications':ab,ti OR 'diabetic complication':ab,ti OR 'complications of diabetes mellitus':ab,ti OR 'diabetes mellitus complication':ab,ti OR 'diabetes mellitus complications':ab,ti

#9 #7 OR #8

#10 'diabetic foot'/exp

#11 'diabetic foot':ab,ti OR 'diabetic feet':ab,ti OR 'feet, diabetic':ab,ti OR 'foot ulcer,

diabetic':ab,ti OR 'foot ulcer':ab,ti

#12 #10 OR #11

#13 #3 OR #6 OR #9 OR #12

#14 'ipswich touch test':ab,ti OR 'touch test':ab,ti OR 'iptt':ab,ti

#15 #13 AND #14

Cochrane Library Search Strategy

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 31055

#2 (Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR (Diabetes Mellitus, Type 1)

#3 MeSH descriptor: [Diabetic Neuropathies] explode all trees

#4 (Diabetic Neuropathy):ti,ab,kw OR (Neuropathies, Diabetic):ti,ab,kw OR (Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathy):ti,ab,kw OR (Autonomic Neuropathies, Diabetic):ti,ab,kw OR (Autonomic Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathies):ti,ab,kw OR (Neuropathies, Diabetic Autonomic):ti,ab,kw OR (Neuropathy, Diabetic Autonomic):ti,ab,kw OR (Symmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Asymmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathy):ti,ab,kw OR (Asymmetric Polyneuropathies, Diabetic):ti,ab,kw OR (Asymmetric Polyneuropathy, Diabetic):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic Asymmetric):ti,ab,kw OR (Polyneuropathy, Diabetic Asymmetric):ti,ab,kw OR (Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Mononeuropathies):ti,ab,kw OR (Mononeuropathies, Diabetic):ti,ab,kw OR (Mononeuropathy, Diabetic):ti,ab,kw OR (Diabetic Mononeuropathy Simplex):ti,ab,kw OR (Diabetic Mononeuropathy Simplices):ti,ab,kw OR (Mononeuropathy Simplex, Diabetic):ti,ab,kw OR (Mononeuropathy Simplices, Diabetic):ti,ab,kw OR (Simplex, Diabetic Mononeuropathy):ti,ab,kw OR

(Simplices, Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Polyneuropathy):ti,ab,kw OR (Diabetic Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic):ti,ab,kw OR (Polyneuropathy, Diabetic):ti,ab,kw 3653

#5 MeSH descriptor: [Diabetes Complications] explode all trees

#6 (Diabetes-Related Complications):ti,ab,kw OR (Diabetes Related Complications):ti,ab,kw OR (Diabetes-Related Complication):ti,ab,kw OR (Diabetic Complications):ti,ab,kw OR (Diabetic Complication):ti,ab,kw OR (Complications of Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus Complication):ti,ab,kw OR (Diabetes Mellitus Complications)

#7 MeSH descriptor: [Diabetic Foot] explode all trees

#8 (Diabetic Feet):ti,ab,kw OR (Feet, Diabetic):ti,ab,kw OR (Foot Ulcer, Diabetic)

#9 (ipswich touch test):ti,ab,kw OR (touch test):ti,ab,kw OR (IPTT)

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#11 #9 AND #10

Web of Science Search Strategy

#1 TS=(Diabetes Mellitus or Diabetes or Diabetes, Type 2 or Type 2 Diabetes Mellitus or Diabetes Mellitus, Type II or Diabetes Mellitus, Type 1)

#2 TS=(Diabetic Neuropathies or Diabetic Neuropathy or Neuropathies, Diabetic or Neuropathy, Diabetic or Diabetic Autonomic Neuropathy or Autonomic Neuropathies, Diabetic or Autonomic Neuropathy, Diabetic or Diabetic Autonomic Neuropathies or Neuropathies, Diabetic Autonomic or Neuropathy, Diabetic Autonomic or Symmetric Diabetic Proximal Motor Neuropathy or Asymmetric Diabetic Proximal Motor Neuropathy or Diabetic Asymmetric Polyneuropathy or Asymmetric Polyneuropathies, Diabetic or Asymmetric Polyneuropathy, Diabetic or Diabetic Asymmetric Polyneuropathies or

Polyneuropathies, Diabetic Asymmetric or Polyneuropathy, Diabetic Asymmetric or Diabetic Mononeuropathy or Diabetic Mononeuropathies or Mononeuropathies, Diabetic or Mononeuropathy, Diabetic or Diabetic Mononeuropathy Simplex or Diabetic Mononeuropathy Simplices or Mononeuropathy Simplex, Diabetic or Mononeuropathy Simplices, Diabetic or Simplex, Diabetic Mononeuropathy or Simplices, Diabetic Mononeuropathy or Diabetic Polyneuropathy or Diabetic Polyneuropathies or Polyneuropathies, Diabetic or Polyneuropathy, Diabetic)

#3 TS=(Diabetes Complications or Diabetes Complication or Diabetes-Related Complications or Diabetes Related Complications or Diabetes-Related Complication or Diabetic Complications or Diabetic Complication or Complications of Diabetes Mellitus or Diabetes Mellitus Complication or Diabetes Mellitus Complications)

#4 TS=(Diabetic Foot or Foot, Diabetic or Diabetic Feet or Feet, Diabetic or Foot Ulcer, Diabetic)

#5 #4 OR #3 OR #2 OR #1

#6 TS=(ipswich touch test or touch test or IPTT)

#7 #6 AND #5

China National Knowledge Infrastructure (CNKI) Search Strategy

检索式 A: (((主题=糖尿病 或者 题名=糖尿病 或者 v_subject=中英文扩展(糖尿病) 或者 title=中英文扩展(糖尿病)) 或者 (主题=糖尿病足 或者 题名=糖尿病足 或者 v_subject=中英文扩展(糖尿病足) 或者 title=中英文扩展(糖尿病足))) 或者 ((主题=糖尿病周围神经病变 或者 题名=糖尿病周围神经病变 或者 v_subject=中英文扩展(糖尿病周围神经病变) 或者 title=中英文扩展(糖尿病周围神经病变)) 或者 (主题=糖尿病并发症 或者 题名=糖尿病并发症 或者 v_subject=中英文扩展(糖尿病并发症) 或者 title=中英文扩展(糖尿病并发症)))) 并且 (((((主题=中英文扩展(touch test) 或者 题名=中英文扩展(touch test) 或者 v_subject=touch test 或者 title=touch test) 或者 (主题=中英文扩展(Ipswich Touch Test) 或者 题名=中英文扩展(Ipswich Touch Test) 或者

v_subject=Ipswich Touch Test 或者 title=Ipswich Touch Test)) 或者 ((主题=伊普斯维奇触摸测试 或者 题名=伊普斯维奇触摸测试 或者 v_subject=中英文扩展(伊普斯维奇触摸测试) 或者 title=中英文扩展(伊普斯维奇触摸测试)) 或者 (主题=中英文扩展(IPTT) 或者 题名=中英文扩展(IPTT) 或者 v_subject=IPTT 或者 title=IPTT))) 或者 ((关键词=轻触 或者 keyword=中英文扩展(轻触)) 或者 (关键词=轻触测试 或者 keyword=中英文扩展(轻触测试)))) 或者 ((题名=触摸 或者 Title=中英文扩展(触摸)) 或者 (题名=触摸测试 或者 Title=中英文扩展(触摸测试)))) (模糊匹配)

Wan Fang Database Search Strategy

主题:((糖尿病)+主题:(糖尿病足)+主题:(糖尿病周围神经病变)+全部:(糖尿病并发症))*主题:((touch test)+主题:(IPTT)+主题:(Ipswich Touch Test)+全部:(伊普斯维奇触摸测试))

China Biology Medicine disc (CBM) Search Strategy

#1 "糖尿病"[不加权:扩展]

#2 "糖尿病足"[常用字段:智能]

#3 "糖尿病神经病变"[常用字段:智能]

#4 "糖尿病并发症"[常用字段:智能]

#5 (#4) OR (#3) OR (#2) OR (#1)

#6 "touch"[常用字段:智能] AND "test"[常用字段:智能]

#7 "IPTT"[常用字段:智能]

#8 "Ipswich"[常用字段:智能] AND "Touch"[常用字段:智能] AND "Test"[常用字段:智能]

#9 "伊普斯维奇触摸测试"[常用字段:智能]

#10 "轻触"[常用字段:智能]

#11 "轻触测试"[常用字段:智能]

#12 "触摸"[常用字段:智能]

#13 "触摸测试"[常用字段:智能]

#14 (#13) OR (#12) OR (#11) OR (#10) OR (#9) OR (#8) OR (#7) OR (#6)

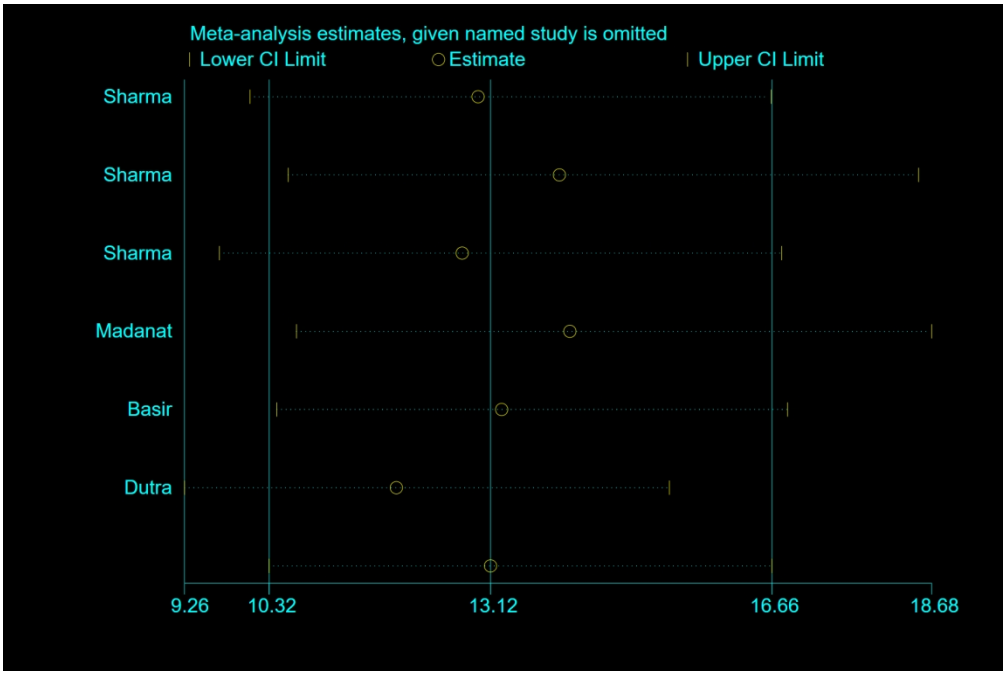
#15 (#14) AND (#5)

```
. diagma tp fp fn tn, qe(qi)

Input form: TP FP FN TN assumed
Note: Weights are from Doi's quality effects model
Studies included: 6
Participants included: 1493
Prevalence of disease: 19.7%
Heterogeneity (I-squared): 40.5%
Pub bias (LFK index): -1.7, minor asymmetry
```

	Estimate	95% Conf.	Interval
Sens	.77	.688	.836
Spec	.957	.928	.975
LR+	18.064	10.748	30.358
LR-	.24	.167	.346
DOR	75.239	39.898	141.887
AUC	.897	.863	.923

The results of sensitivity and specificity of IPTT in the diagnosis of DPN



Supplementary Files 3. Sensitivity analysis

644x429mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Neurology, Public health, Diabetes and endocrinology
Keywords:	Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH, Diabetic foot < DIABETES & ENDOCRINOLOGY

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: Diabetic peripheral neuropathy (DPN) is one of the most important risk factors of diabetic foot ulcers (DFU), and early screening and treatment of DPN are crucial. The Ipswich Touch Test (IPTT) is a new method for screening for DPN and, compared with traditional methods, is more simple to operate and requires no equipment. However, the screening accuracy of IPTT in DPN patients has not been well characterized. We aim to conduct a systematic review and meta-analysis to characterize the sensitivity and specificity of IPTT compared to traditional methods and to understand the potential screening value of IPTT.

Design： Systematic review and meta-analysis.

Data sources： PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Database (CBM) up to April 16, 2020.

Methods: Stata version 15.1 software was used for analysis, and the screening value of IPTT in DPN was described using 10g-MF, NDS, Pin prick, 128Hz tuning fork, and ankle reflex as reference standards. Sensitivity, specificity, and other measures of accuracy of IPTT for screening DPN were pooled based on a quality effects model. The protocol was registered with PROSPERO (42020168420).

Results: Of the 441 records retrieved, seven studies were evaluated for the screening value of IPTT. Five studies with 10g-MF as the reference standard were included in the meta-analysis, and the pooled sensitivity and specificity were 0.78 (95 % CI 0.65–0.87) and 0.95(95 % CI 0.89–0.98), respectively, and AUC was 0.93. Compared with VPT, IPTT showed a sensitivity between 0.76 and 1, and a specificity between 0.90 and 0.97. Compared with NDS, IPTT showed a sensitivity between 0.53 and 1, and a specificity between 0.90 and 0.97. Compared with Pin prick, IPTT showed a

sensitivity and specificity of 0.8 and 0.88, respectively. Compared with 128Hz tuning fork, IPTT showed a sensitivity and specificity of 0.4 and 0.27, respectively. Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97.

Conclusions: IPTT shows a high degree of agreement with other commonly used screening tools for DPN screening. It can be used clinically, especially in remote areas and in primary medical institutions, and by self-monitoring patients. More high-quality studies are needed to assess and promote more effective screening practices.

Prospero: Registration Number is CRD (42020168420)

Strengths and limitations of this study

- This is the first meta-analysis to explore the potential screening value of IPTT in DPN.
- A quality effects model was used to achieve optimal error estimation in the data analysis.
- A Doi plots and Luis Furuya-Kanamori (LFK) index were used to assess publication bias.
- Although we systematically and comprehensively studied the current evidence of IPTT screening in DPN screening, the number of original studies was very limited, and the existing conclusions were based on these 7 original studies. Therefore, readers should therefore proceed with caution.

Keywords: Ipswich Touch Test, Diabetic peripheral neuropathy, Meta-analysis

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common long-term complication and the most important risk factor for the occurrence of diabetic foot ulcers (DFU).[1-4] DPN affects up to 50% of people with diabetes,[5,6] with chronic painful neuropathy affecting up to 26%.[7] In the early stage of DPN, the symptoms lack specificity, and about half of patients with diabetes cannot recognize the injury to the lower extremities.[8,9] Once the patient has symptoms such as limb numbness and pain, it signals that pathological changes have occurred in the peripheral nerves and have advanced into the

irreversible stage. If not treated promptly, serious tissue damage, such as foot ulcers, amputation, and even death, may occur.[10,11] Studies have shown that early screening and detection of peripheral neuropathy can not only slow down the DPN process, but also effectively prevent DFU.[12] Therefore, early screening and treatment of DPN is very important.

At present, the screening value of 10g monofilament (10g-MF), Vibration perception threshold (VPT), and 128Hz tuning fork in DPN has been widely recognized.[13] Compared with VPT and 128Hz tuning forks, 10g-MF is the most widely used screening tool because it is more simple, objective, and easy to carry, although it requires a calibration facility to confirm that the vertical pressure of the monofilament used when bending is 10g.[14-16] Commercially available 10g-MF devices exhibit significant variability within and between devices of different manufacturers and their actual bending force varies widely from their designated 10g value. When used they have a short service life where the instrument is within 10% of their initial bending force which is not usually the stated 10g of force.[17,18] Meanwhile, medical personnel are required to be trained before using the device, and screening is limited to hospitals or clinics. For clinics and communities in remote areas, medical personnel may lack the device or the training to screen patients for DPN, resulting in a missed opportunity for patients to receive the best treatment. In recent years, Dr. Rayman proposed the Ipswich Touch Test (IPTT), which only requires the physician's index finger. During this test, the patient is required to close their eyes while the physician lightly rests their finger on each of the patient's first, third, and fifth toes for 1 to 2 seconds. Patients are instructed to respond with a "yes" when they feel the physician's touch. Compared with the current methods, IPTT requires no equipment, is more convenient and effective, and can be performed by doctors, nurses, and even family caregivers after training.[19] IPTT can be applied to inpatients, outpatients, community patients, self-monitoring patients at home, and to areas lacking more advanced equipment.[20,21] Currently, IPTT has been applied in the United Kingdom, Spain, Brazil, and Saudi Arabia,[19,22-26] and was approved by the American Diabetes Association in 2015.[20] The 2019 guidelines of the International Working Group on the Diabetic Foot also suggest that IPTT should be used for DPN screening in patients with diabetes in the absence of 10g-MF.[27] Although these studies have achieved satisfactory results, they have not been widely promoted and applied globally.

Previous studies have reported differences in the results of the screening value of DPN. However, neither a meta-analysis nor a systematic review has been conducted on the screening value of IPTT.

In this study, we aimed to conduct a comprehensive and systematic literature review to systematically evaluate the potential screening value of IPTT in DPN, and provide evidence and guidance for the clinical application value of IPTT.

METHODS

The Joanna Briggs Institute (JBI) protocol[28] has been registered with PROSPERO, the International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination (Registration Number is CRD (42020168420). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[29].

Data Sources and Searches

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Biomedical Literature Database (CBM) for reports published before April 16, 2020. For included studies with insufficient data, we emailed the authors to ask if they would provide data for our study. With this strategy, we combined search terms for applied technique (Ipswich touch test, touch test, IPTT) and disease (Diabetic peripheral neuropathy, diabetic foot, diabetic foot ulcer, Diabetes Mellitus, diabetic complications). The study design and published language were not limited. In addition, we conducted a manual search, including searching through conference papers and gray literature, and the references of all included studies were examined. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database. A detailed search strategy is provided in “Supplementary files 1”. All analyses were based on previously published studies; thus, no ethical approval and patient consent were required.

Inclusion and Exclusion Criteria

Previously published studies were included in this meta-analysis if: (1) the study examined the screening accuracy of the IPTT test for detecting DPN; (2) all the research subjects were patients

with diabetes, and; (3) IPTT was included as an index test. Studies were excluded from the meta-analysis if the studies had incomplete data sets or were other than original reports (commentaries/reviews). The age, sex, region, and race of the subjects were not restricted. The published language was not limited.

Data Extraction and Quality Assessment

We imported initial search records from databases into NoteExpress V3.2.0.7535 literature management software. Two reviewers independently screened titles and abstracts of all the included literature, following the inclusion and exclusion criteria. After screening the abstract, the full text was read in detail. Any discrepancies were resolved by discussion. The following information was extracted from the eligible studies: study characteristics (author, publication year, study period, country, reference standard, setting, operators), participant characteristics (sample number, range), and outcome indicators (sensitivity, specificity, true positive number (TP), false positive number (FP), false negative number (FN), true negative number (TN)). Missing data were supplemented by contacting authors wherever possible.

The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS), it is a methodological quality assessment scale, and includes 14 items[30]. Quality items were weighted equally with 1 point awarded for each of the 14 items. The quality score was then calculated by summing the points awarded for each question (maximum sum 14). This score was then normalized by dividing the sum by the highest score of the listed studies, thereby ranking the studies from 1 down to a minimum of 0.[31] Data extraction and quality assessment was performed independently by two reviewers. Differences were reconciled through discussion until a consensus was reached on the item in question.

Data Synthesis

The likelihood ratio is an independent indicator to assess authenticity, which can simultaneously reflect sensitivity and specificity. When the PLR is >10 or the NLR is <0.1, the probability of diagnosing or excluding a certain disease increases significantly. The DOR with 95% CI was also

calculated. For each summary statistic, a 95% confidence interval was computed. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and corresponding 95% confidence interval (95% CI) were obtained using the quality effects model, it is the synthesis model for diagnostic odds ratios within the split component synthesis method.[32,33] Relevant studies have proven that this model is superior to the traditional random effects model and fixed effects model.[34-36] The quality scores were used to redistribute inverse variance weights based on study deficiencies via the quality effects model,[37,38] the software by using Stata, version15.1 (Stata Corp, College Station, TX)

Since the number of studies included affects the Q test, we used the I^2 statistic to evaluate the magnitude of heterogeneity since the value of the I^2 statistic will not change with the number of studies included and the results of heterogeneity test are more reliable, An $I^2 \geq 50\%$ indicates the existence of significant heterogeneity.[39,40] Publication bias was assessed with Doi plots and Luis Furuya-Kanamori (LFK) index, the Doi plot uses a rank-based measure (Z score) of precision (instead of the standard error) and plots it against the effect size, it can visualize asymmetry, and the LFK index quantifies the extent of Doi plot asymmetry by averaging half of the sum of the Z score plus the normalized effect size across the meta-analysis, which can detect and quantify the asymmetry in the Doi plots. The closer the value of the LFK index is to zero, the more symmetrical the Doi plot.[41] LFK index values outside the interval of -1 and +1 are deemed consistent with asymmetry.[41] Related studies have shown that these methods can markedly improve the ability of researchers to detect bias in a meta-analysis. [41]

Patient and public involvement

Since the data in this study were all from previously published studies, patients and the public were not involved in this research.

RESULTS

Study Selection

Our initial search resulted in a total of 441 records: 437 from database searching and four records

from mshuianual searches of references. After duplicates were removed, 242 records were identified, and 220 records were excluded as irrelevant. After reading the full-text articles, 7 studies met the inclusion criteria (Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.). Two studies were excluded for lacking necessary data for meta-analysis. Finally, five studies with 6 datasets were included in the final meta-analysis, involving a total of 1162 patients.[22-26]

Characteristics and Quality of the Included Studies

The characteristics of the included studies are presented in Table 1. The 7 studies included a total of 1,510 participants with diabetes and were published between 2011 and 2020.[19,22-27] To explore the accuracy of IPTT in DPN screening, 10g-MF, VPT, NDS, pin prick, 128Hz tuning fork, and ankle reflex were used as the reference standard. The research setting included homes of patients, clinics, care centers, and outpatient centers, and the assessors included doctors, nurses, and family caregivers.

We assessed the methodological quality of the studies using QUADAS. The assessment results of the research methodological quality of each study are presented in Figures 2.[42]

Table 1. Basic characteristics of the included studies.

Study	Year	Country	n	Setting	Operators	Quality score(Qi)	Reference standard	TP	FP	FN	TN	Se(%)	Sp (%)
Sharma[22]	2012	UK	130	home	families	0.074	10g-MF	24	4	6	96	80.0	96.0
Sharma[23]	2014	UK	331	home	families	0.714	10g-MF	65	15	18	233	78.3	93.9
				clinic	doctors/ nurses	0.786	10g-MF	67	9	16	239	81.2	96.4
Amal Madanat[24]	2015	Saudi Arabia	351	care centers	doctors/ nurses	0.357	10g-MF	29	6	28	288	51.0	98.0
							VPT	48	24	9	270	85	92
							NDS	30	9	27	285	53	97
I.S, Basir[25]	2020	Spain	100	care centers	doctors/ nurses	0.429	10g- MF	4	30	1	65	80.0	68.0
							Pin prick	4	1	11	84	80.0	88.0
							Tuning fork 128Hz	2	3	69	26	40.0	27.0
							Ankle reflex	1	4	2	93	20.0	97.0
Dutra[26]	2020	Brasília	250	outpatient centre	doctors/ nurses	0.643	10g-MF	30	5	6	209	83.3	97.7
Rayman[19]	2011	UK	265	clinic	-	-	VPT	-	-	-	-	76.0	90.0
Bowling[27]	2012	UK	83	clinic	doctors/ nurses	-	VPT	-	-	-	-	100	96.6
							NDS	-	-	-	-	100	90.3

Se, Sensitivity; Sp, Specificity

Screening Accuracy

In the included studies, the researchers used a variety of different test methods as the standard to observe the sensitivity and specificity of IPTT for screening for DPN, such as 10g-MF, VPT, NDS, tuning fork 128Hz, and ankle reflex. The differences in the sensitivity and specificity of IPTT obtained by using different test methods as reference standards are presented. In general, when 10g-MF and VPT were used as reference standards, the sensitivity and specificity of IPTT were relatively high. For the 5 studies comprising 6 data pools that used 10g-MF as the reference standard, the sensitivity ranged from 51.0% - 83.3%, and the specificity ranged from 68.0 - 98.0%.[22-26] For the 3 studies that used VPT as a reference standard, the sensitivity ranged from 76.0 - 100.0%, and the specificity ranged from 90.0 - 96.6%. Using neuropathy disability scores (NDS) as the reference standard, the sensitivity of IPTT to be 0.53, and the specificity to be 0.97. Compared with the pin prick, the sensitivity and specificity of IPTT were 0.8 and 0.88, respectively.[24] Compared with 128Hz tuning fork, the sensitivity and specificity of IPTT were only 0.4 and 0.27, respectively.[25] Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97(Table 1).[25]

Meta-analysis Results Using 10g-MF as the Reference Standard

Screening Accuracy

In the literature we retrieved, there were a total of five studies with IPTT as the target test and 10g-MF as the reference standard.[22-26] Among these five studies, one study contained two datasets because it was conducted at the patient's homes and in the clinic.[22] Therefore, six datasets were included to evaluate the overall effect of IPTT in the screening of DPN. [22-26] The combined sensitivity and specificity were 0.77 (95％CI 0.69–0.84) and 0.96 (95％CI 0.93–0.98), respectively.

The results show I - squared is 40.5%. In addition, the DOR was 75.24(39.90-141.89). The SROC analysis for the studies yielded an overall weighted area under the curve of 0.897(0.86-0.92) (Figure 3; Supplementary Files 2;Table 2).

Table 2. Meta-analysis of screening accuracy under the quality effect model

Variables	Se (95% CI)	Sp (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Pooled value	0.77(0.69-0.84)	0.96(0.93-0.98)	18.06 (10.75-30.36)	0.24(0.17-0.35)	75.24(39.90-141.89)	0.897(0.86-0.93)

Se, Sensitivity; Sp, Specificity; CI: Confidence Interval.

Publication Bias

Minor asymmetry was present in the Doi plot and the results of the LFK index also suggested minor negative asymmetry of the Doi plot (LFK index =-1.68), indicating the publication bias existed between the studies (Figure 4).

DISCUSSION

DPN is the most important risk factor for the occurrence of DFU and one of the more common chronic complications associated with diabetes. However, it is often ignored. Once the patient develops DPN, it is likely to cause diabetic foot ulcers, gangrene, and even amputation, and many patients experience numbness and tingling in their limbs. Early identification of DPN can greatly reduce the burden of chronic diseases on society. In this study, we systematically reviewed the relevant literature on the identification of DPN by IPTT. A total of 7 studies were included, involving 1,510 participants with diabetes to explore the value of IPTT screening. Previous studies have disputed the diagnostic value of IPTT, mainly due to the use of different test methods, such as VPT, NDS, pinprick, tuning fork 128Hz, and ankle reflex, as the reference standard, compared with NDS, acupuncture, 128Hz tuning fork, and ankle reflex, IPTT has higher screening accuracy when 10g-MF and VPT were used as the reference standard.[10,19,20] Basir et al. observed that when the 128Hz tuning fork was used as a reference standard, the sensitivity and specificity of IPTT were only 40% and 27%, respectively. This may be due to the lower predictive level of the tuning fork compared to the monofilament. However, Miller et al observed that combining a tuning fork with a monofilament would result in a more effective evaluation.[21] Regarding the quality of the current studies, some studies lacked rigor in study design, such as the interval between target tests and unclear reference standard tests, and most studies failed to describe the reference methods in detail.

The overall quality of the included studies was rated as low to medium quality.

Compared with 10g-MF, the results of the meta-analysis found the combined sensitivity and specificity of IPTT to be 0.77(95％CI 0.69-0.84) and 0.96(95％CI 0.93-0.98), respectively, and the AUC to be 0.897(95％CI 0.86-0.93). The results indicated that IPTT has a moderate to high level of sensitivity and a high level of specificity for screening DPN. In our study, the PLR and the NLR were 18.06 (95% CI 10.75-30.36) and 0.24(95% CI 0.17-0.35), respectively, it means that the screening accuracy of IPTT in DPN patients was nearly 18 times of the healthy peoples, but with 24% error rate. A DOR equal to 1 indicated that a test was unable to distinguish between patients with or without the disease. Our study yielded a DOR value of 75.24(95％CI 39.90-141.89), indicating that IPTT had a certain accuracy in the diagnosis of patients with DPN. We also found that when VPT is used as a reference standard, IPTT shows a higher sensitivity and specificity. At present, 10g-MF and VPT are the most widely used clinical screening methods for DPN. Basir et al. explored the accuracy of using IPTT in detecting neuropathy in patients with small fiber and large fiber neuropathy, and found that there was no difference between IPTT and the gold standard, indicating that IPTT can be used as an alternative assessment method.[25] Therefore, the current evidence shows that IPTT has a high screening value for DPN and can be used for preliminary screening of DPN in areas lacking more advanced equipment.

Heterogeneity is an important factor of this meta-analysis.[43] In this study, we chose the quality effects model because it has been proven to be significantly better than the traditional random effects model and fixed effects model at effectively avoiding the problem of high heterogeneity caused by statistical analysis. When 10g-MF was used as the reference standard, the I^2 was only 40.5%, indicating there was good consistency among the five studies included in the meta-analysis. In addition, the existence of heterogeneity may be related to other factors, such as differences in research methodology, operators, or other factors. Due to the limited number of included studies, we did not analyze the heterogeneity through subgroup analysis in this study. In terms of methodology, although we systematically and comprehensively studied the current evidence of

using IPTT for DPN screening, the number of original studies is very limited, and the current conclusions are based only on these seven studies. Therefore, caution should be taken when popularizing them. About using other test methods as the reference standard (except 10g-MF), we only described the relevant indicators as there were too few related studies to merge data. In addition, despite our efforts to conduct a thorough search for eligible studies, publication bias was detected. Thus, the pooled effect may have been overstated, this was also one of the limitations of our study.

Studies have shown that routine foot examinations and rapid risk stratification are often difficult to implement in busy primary care institutions. Additionally, the lack of awareness of standardized testing for DPN amongst healthcare professionals is a concern, which may be due to a shortage of material and personnel resources in primary care institutions. This is concerning because identifying foot neuropathy and the patients at risk for ulceration has been shown to prevent the incidence of foot ulcers.[44-46] IPTT is a new method for screening DPN that does not require any tools and can be carried out after minimal training. It is not affected by time, venue, or its operators.[20] The advancement of IPTT is of great significance for the early screening of DPN to impede the progression of diabetic foot ulcers, as it can be used to quickly and reliably screen and manage patients at high risk for ulceration, especially in remote areas or places lacking screening tools.[47,48] Kerry et al. reported that in the first year IPTT was introduced as a screening tool, the relative risk reduction (RRR) of DFU was 64%, and in the second year, the RRR was 70%, thereby reducing hospital-acquired foot ulcers in patients with diabetes by two-thirds and negating the excess risk associated with diabetes.[20,49-51] Meanwhile, it can effectively improve patients' disease-related knowledge, which plays a positive role in promoting the self-management of patients and their families. At the same time, IPTT has a predictive effect on diabetic foot ulcers and reduces delays in patient visits.[21] However, more thorough studies are needed for verification.

Most of the literature on IPTT is focused on screening tests and some commentary-type studies, and the number of studies is small. These studies were carried out in the United Kingdom, Spain, Brazil, and Saudi Arabia, and although they achieved satisfactory results, have not been carried out globally. However, it has not been applied in developing countries such as China. China is a country with a large population and a relatively small number of medical personnel, especially in some

remote areas where the medical allocation is in short supply. In these areas, the application and promotion of IPTT can effectively alleviate the challenges associated with the allocation of medical resources and play an important role in the management of patients with diabetes. IPTT has also recently been approved for use in a number of countries.[21,24-26] However, Kempegowda et al. reported that 88.4% of physicians are not familiar with IPTT. Therefore, we suggest that IPTT be further promoted amongst physicians and medical staff, especially in remote areas and areas lacking screening tools.[36] Future large-scale, high-quality, and multi-center studies on populations of different ethnicities will verify the potential applicability of IPTT alone or in combination with other DPN screening methods.

CONCLUSIONS

In summary, IPTT shows a high degree of agreement with commonly used screening tools for DPN, it can be used clinically, especially in remote areas and primary medical institutions, and self-monitoring patients. This is also the first meta-analysis of the accuracy of IPTT identification of DPN, and a systematic quantitative evaluation of its screening value, which can provide evidence for the clinical application of IPTT in the future. However, due to a limited number of studies of low or medium quality from limited geographical areas, more high-quality studies are needed to promote more effective screening practices.

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Author contributions

ZN conducted the database search, screened and extracted data for the meta-analysis, prepared extracted data for the procedures, and had primary responsibility in writing this article. LXY, ZJ

and ZF performed statistical analysis and contributed to article screening, data collection and extraction. XJC, ZQH, and LJH contributed to the discussion and editing. XJC and CJR critically revised the draft manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Competing interests

The authors state that they have no conflict of interest.

Patient consent for publication

Not required. All analyses were conducted based on previously published studies. Accordingly, there was no patient or public involvement in this study. Ethical approval was not required since it was a systematic review of the published literature.

Data availability statement

Data are available in a public, open access repository. There are no data in this work. Data are available on reasonable request. Data can be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information.

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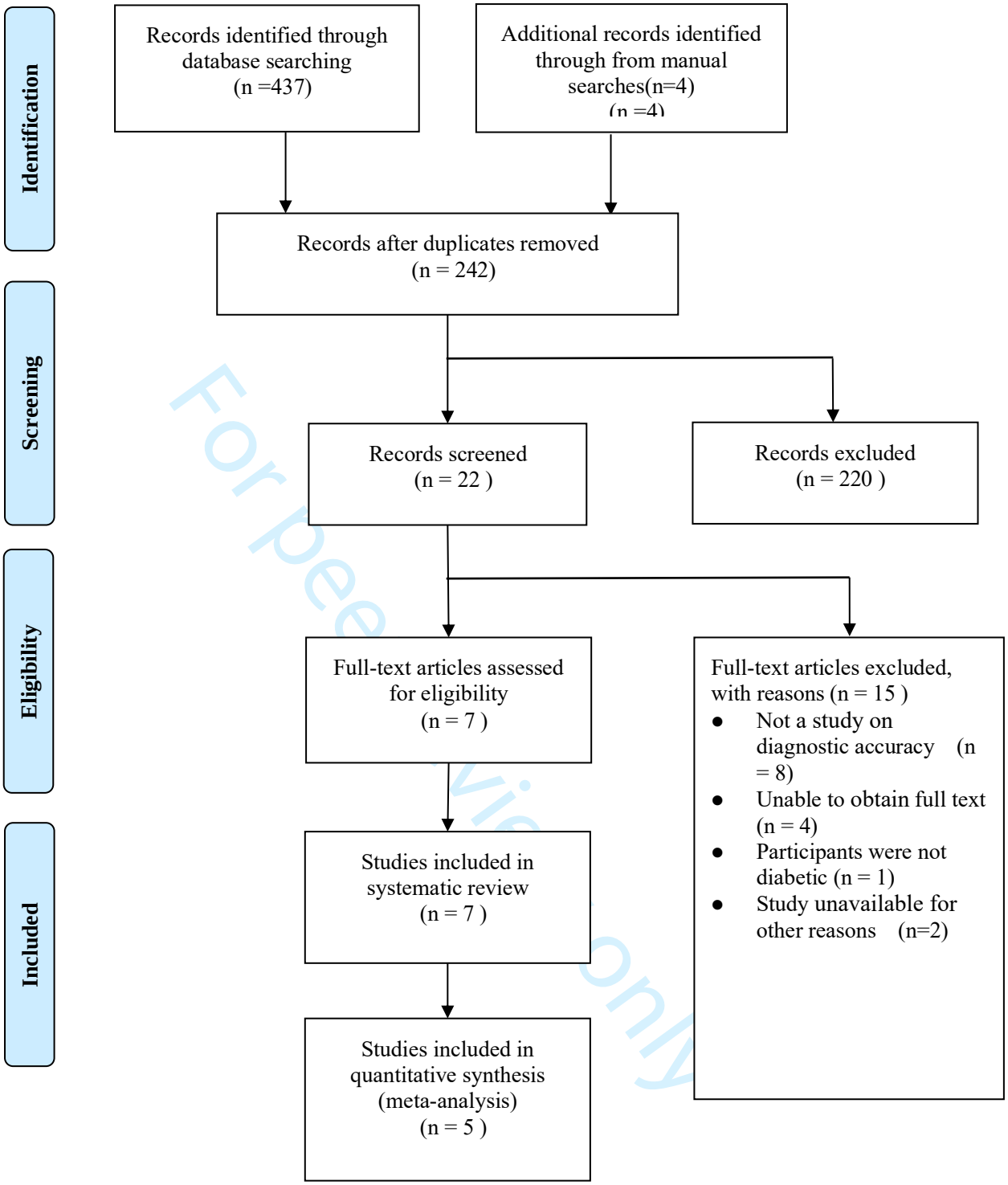

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2. Quality assessment of the included studies

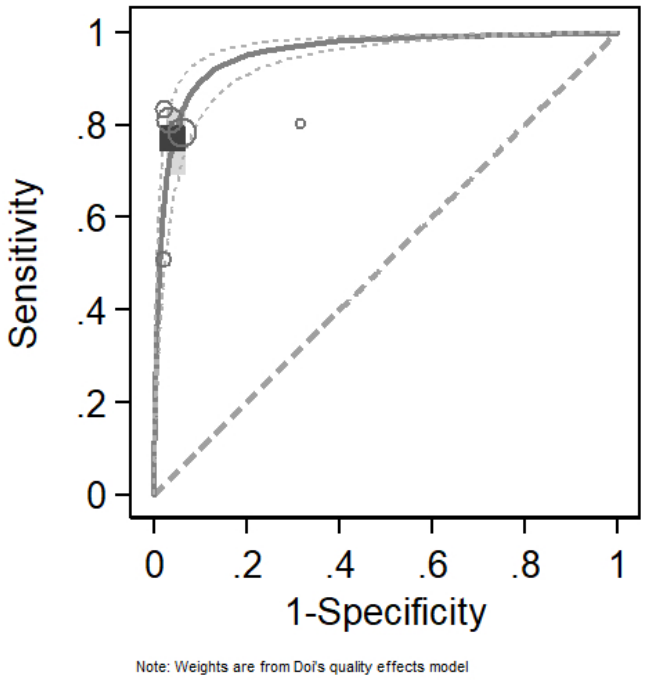

Figure 3. Sensitivity and specificity of IPTT in the diagnosis of DPN

255x185mm (72 x 72 DPI)

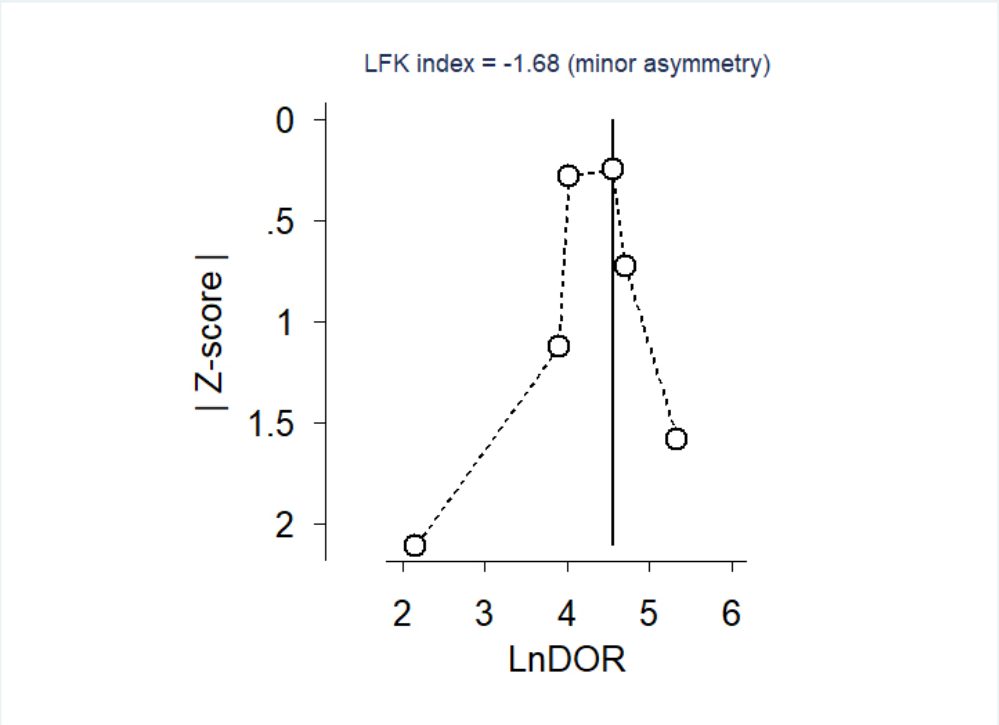

Figure 4. Doi plot and LFK index.

255x185mm (72 x 72 DPI)

Appendix S1

Search Strategy in PubMed, Embase, Cochrane Library, Web of Science, CNKI, CMB, Wanfang database.

PubMed Search Strategy

#1 Search: "Diabetes Mellitus"[Mesh] Sort by: Most Recent

#2 Search: ((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract])

#3 Search: "Diabetic Neuropathies"[Mesh] Sort by: Most Recent

#4 Search: ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR

(Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract])

#5 Search: "Diabetes Complications"[Mesh] Sort by: Most Recent

#6 Search:

#7 Search: "Diabetic Foot"[Mesh] Sort by: Most Recent

#8 Search: (((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])

#9 Search: ((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract])

#10 Search: (((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic

Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract]))

#11 Search: (((((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR

(Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])))) AND (((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract]))

Embase Search Strategy

#1 'diabetes mellitus'/exp

#2 'diabetes, type 2':ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'diabetes mellitus, type ii':ab,ti OR 'diabetes mellitus, type 1':ab,ti

#3 #1 OR #2

#4 'diabetic neuropathy'/exp

#5 'diabetic neuropathy':ab,ti OR 'neuropathies, diabetic':ab,ti OR 'neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathy':ab,ti OR 'autonomic neuropathies, diabetic':ab,ti OR 'autonomic neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathies':ab,ti OR 'neuropathies, diabetic autonomic':ab,ti OR 'neuropathy, diabetic autonomic':ab,ti OR 'symmetric diabetic proximal motor neuropathy':ab,ti OR 'asymmetric diabetic proximal motor neuropathy':ab,ti OR 'diabetic asymmetric polyneuropathy':ab,ti OR 'asymmetric polyneuropathies, diabetic':ab,ti OR 'asymmetric polyneuropathy, diabetic':ab,ti OR 'diabetic asymmetric polyneuropathies':ab,ti OR 'polyneuropathies, diabetic asymmetric':ab,ti OR 'polyneuropathy, diabetic asymmetric':ab,ti OR 'diabetic mononeuropathy':ab,ti OR 'diabetic mononeuropathies':ab,ti OR 'mononeuropathies, diabetic':ab,ti OR 'mononeuropathy, diabetic':ab,ti OR 'diabetic mononeuropathy simplex':ab,ti OR 'diabetic mononeuropathy simplices':ab,ti OR 'mononeuropathy simplex, diabetic':ab,ti OR 'mononeuropathy simplices, diabetic':ab,ti OR 'simplex, diabetic mononeuropathy':ab,ti OR 'simplices, diabetic mononeuropathy':ab,ti OR 'diabetic polyneuropathy':ab,ti OR 'diabetic polyneuropathies':ab,ti OR 'polyneuropathies, diabetic':ab,ti OR 'polyneuropathy, diabetic':ab,ti

#6 #4 OR #5

#7 'diabetic complication'/exp

#8 'diabetes complication':ab,ti OR 'diabetes-related complications':ab,ti OR 'diabetes related complications':ab,ti OR 'diabetes-related complication':ab,ti OR 'diabetic complications':ab,ti OR 'diabetic complication':ab,ti OR 'complications of diabetes mellitus':ab,ti OR 'diabetes mellitus complication':ab,ti OR 'diabetes mellitus complications':ab,ti

#9 #7 OR #8

#10 'diabetic foot'/exp

#11 'diabetic foot':ab,ti OR 'diabetic feet':ab,ti OR 'feet, diabetic':ab,ti OR 'foot ulcer,

diabetic':ab,ti OR 'foot ulcer':ab,ti

#12 #10 OR #11

#13 #3 OR #6 OR #9 OR #12

#14 'ipswich touch test':ab,ti OR 'touch test':ab,ti OR 'iptt':ab,ti

#15 #13 AND #14

Cochrane Library Search Strategy

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 31055

#2 (Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR (Diabetes Mellitus, Type 1)

#3 MeSH descriptor: [Diabetic Neuropathies] explode all trees

#4 (Diabetic Neuropathy):ti,ab,kw OR (Neuropathies, Diabetic):ti,ab,kw OR (Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathy):ti,ab,kw OR (Autonomic Neuropathies, Diabetic):ti,ab,kw OR (Autonomic Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathies):ti,ab,kw OR (Neuropathies, Diabetic Autonomic):ti,ab,kw OR (Neuropathy, Diabetic Autonomic):ti,ab,kw OR (Symmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Asymmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathy):ti,ab,kw OR (Asymmetric Polyneuropathies, Diabetic):ti,ab,kw OR (Asymmetric Polyneuropathy, Diabetic):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic Asymmetric):ti,ab,kw OR (Polyneuropathy, Diabetic Asymmetric):ti,ab,kw OR (Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Mononeuropathies):ti,ab,kw OR (Mononeuropathies, Diabetic):ti,ab,kw OR (Mononeuropathy, Diabetic):ti,ab,kw OR (Diabetic Mononeuropathy Simplex):ti,ab,kw OR (Diabetic Mononeuropathy Simplices):ti,ab,kw OR (Mononeuropathy Simplex, Diabetic):ti,ab,kw OR (Mononeuropathy Simplices, Diabetic):ti,ab,kw OR (Simplex, Diabetic Mononeuropathy):ti,ab,kw OR

(Simplices, Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Polyneuropathy):ti,ab,kw OR (Diabetic Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic):ti,ab,kw OR (Polyneuropathy, Diabetic):ti,ab,kw 3653

#5 MeSH descriptor: [Diabetes Complications] explode all trees

#6 (Diabetes-Related Complications):ti,ab,kw OR (Diabetes Related Complications):ti,ab,kw OR (Diabetes-Related Complication):ti,ab,kw OR (Diabetic Complications):ti,ab,kw OR (Diabetic Complication):ti,ab,kw OR (Complications of Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus Complication):ti,ab,kw OR (Diabetes Mellitus Complications)

#7 MeSH descriptor: [Diabetic Foot] explode all trees

#8 (Diabetic Feet):ti,ab,kw OR (Feet, Diabetic):ti,ab,kw OR (Foot Ulcer, Diabetic)

#9 (ipswich touch test):ti,ab,kw OR (touch test):ti,ab,kw OR (IPTT)

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#11 #9 AND #10

Web of Science Search Strategy

#1 TS=(Diabetes Mellitus or Diabetes or Diabetes, Type 2 or Type 2 Diabetes Mellitus or Diabetes Mellitus, Type II or Diabetes Mellitus, Type 1)

#2 TS=(Diabetic Neuropathies or Diabetic Neuropathy or Neuropathies, Diabetic or Neuropathy, Diabetic or Diabetic Autonomic Neuropathy or Autonomic Neuropathies, Diabetic or Autonomic Neuropathy, Diabetic or Diabetic Autonomic Neuropathies or Neuropathies, Diabetic Autonomic or Neuropathy, Diabetic Autonomic or Symmetric Diabetic Proximal Motor Neuropathy or Asymmetric Diabetic Proximal Motor Neuropathy or Diabetic Asymmetric Polyneuropathy or Asymmetric Polyneuropathies, Diabetic or Asymmetric Polyneuropathy, Diabetic or Diabetic Asymmetric Polyneuropathies or

Polyneuropathies, Diabetic Asymmetric or Polyneuropathy, Diabetic Asymmetric or Diabetic Mononeuropathy or Diabetic Mononeuropathies or Mononeuropathies, Diabetic or Mononeuropathy, Diabetic or Diabetic Mononeuropathy Simplex or Diabetic Mononeuropathy Simplices or Mononeuropathy Simplex, Diabetic or Mononeuropathy Simplices, Diabetic or Simplex, Diabetic Mononeuropathy or Simplices, Diabetic Mononeuropathy or Diabetic Polyneuropathy or Diabetic Polyneuropathies or Polyneuropathies, Diabetic or Polyneuropathy, Diabetic)

#3 TS=(Diabetes Complications or Diabetes Complication or Diabetes-Related Complications or Diabetes Related Complications or Diabetes-Related Complication or Diabetic Complications or Diabetic Complication or Complications of Diabetes Mellitus or Diabetes Mellitus Complication or Diabetes Mellitus Complications)

#4 TS=(Diabetic Foot or Foot, Diabetic or Diabetic Feet or Feet, Diabetic or Foot Ulcer, Diabetic)

#5 #4 OR #3 OR #2 OR #1

#6 TS=(ipswich touch test or touch test or IPTT)

#7 #6 AND #5

China National Knowledge Infrastructure (CNKI) Search Strategy

检索式 A: (((主题=糖尿病 或者 题名=糖尿病 或者 v_subject=中英文扩展(糖尿病) 或者 title=中英文扩展(糖尿病)) 或者 (主题=糖尿病足 或者 题名=糖尿病足 或者 v_subject=中英文扩展(糖尿病足) 或者 title=中英文扩展(糖尿病足))) 或者 ((主题=糖尿病周围神经病变 或者 题名=糖尿病周围神经病变 或者 v_subject=中英文扩展(糖尿病周围神经病变) 或者 title=中英文扩展(糖尿病周围神经病变)) 或者 (主题=糖尿病并发症 或者 题名=糖尿病并发症 或者 v_subject=中英文扩展(糖尿病并发症) 或者 title=中英文扩展(糖尿病并发症)))) 并且 (((((主题=中英文扩展(touch test) 或者 题名=中英文扩展(touch test) 或者 v_subject=touch test 或者 title=touch test) 或者 (主题=中英文扩展(Ipswich Touch Test) 或者 题名=中英文扩展(Ipswich Touch Test) 或者

v_subject=Ipswich Touch Test 或者 title=Ipswich Touch Test)) 或者 ((主题=伊普斯维奇触摸测试 或者 题名=伊普斯维奇触摸测试 或者 v_subject=中英文扩展(伊普斯维奇触摸测试) 或者 title=中英文扩展(伊普斯维奇触摸测试)) 或者 (主题=中英文扩展(IPTT) 或者 题名=中英文扩展(IPTT) 或者 v_subject=IPTT 或者 title=IPTT))) 或者 ((关键词=轻触 或者 keyword=中英文扩展(轻触)) 或者 (关键词=轻触测试 或者 keyword=中英文扩展(轻触测试)))) 或者 ((题名=触摸 或者 Title=中英文扩展(触摸)) 或者 (题名=触摸测试 或者 Title=中英文扩展(触摸测试)))) (模糊匹配)

Wan Fang Database Search Strategy

主题:((糖尿病)+主题:(糖尿病足)+主题:(糖尿病周围神经病变)+全部:(糖尿病并发症))*主题:((touch test)+主题:(IPTT)+主题:(Ipswich Touch Test)+全部:(伊普斯维奇触摸测试))

China Biology Medicine disc (CBM) Search Strategy

#1 "糖尿病"[不加权:扩展]

#2 "糖尿病足"[常用字段:智能]

#3 "糖尿病神经病变"[常用字段:智能]

#4 "糖尿病并发症"[常用字段:智能]

#5 (#4) OR (#3) OR (#2) OR (#1)

#6 "touch"[常用字段:智能] AND "test"[常用字段:智能]

#7 "IPTT"[常用字段:智能]

#8 "Ipswich"[常用字段:智能] AND "Touch"[常用字段:智能] AND "Test"[常用字段:智能]

#9 "伊普斯维奇触摸测试"[常用字段:智能]

#10 "轻触"[常用字段:智能]

#11 "轻触测试"[常用字段:智能]

#12 "触摸"[常用字段:智能]

#13 "触摸测试"[常用字段:智能]

#14 (#13) OR (#12) OR (#11) OR (#10) OR (#9) OR (#8) OR (#7) OR (#6)

#15 (#14) AND (#5)

```
. diagma tp fp fn tn, qe(qi)

Input form: TP FP FN TN assumed
Note: Weights are from Doi's quality effects model
Studies included: 6
Participants included: 1493
Prevalence of disease: 19.7%
Heterogeneity (I-squared): 40.5%
Pub bias (LFK index): -1.7, minor asymmetry
```

	Estimate	95% Conf.	Interval
Sens	.77	.688	.836
Spec	.957	.928	.975
LR+	18.064	10.748	30.358
LR-	.24	.167	.346
DOR	75.239	39.898	141.887
AUC	.897	.863	.923

The results of sensitivity and specificity of IPTT in the diagnosis of DPN

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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Secondary Subject Heading:	Neurology, Public health, Diabetes and endocrinology
Keywords:	Diabetic neuropathy < DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH, Diabetic foot < DIABETES & ENDOCRINOLOGY

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

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Application of the Ipswich Touch Test for Diabetic Peripheral Neuropathy Screening: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: Diabetic peripheral neuropathy (DPN) is one of the most important risk factors of diabetic foot ulcers (DFU), and early screening and treatment of DPN are crucial. The Ipswich Touch Test (IPTT) is a new method for screening for DPN and, compared with traditional methods, is more simple to operate and requires no equipment. However, the screening accuracy of IPTT in DPN patients has not been well characterized. We aim to conduct a systematic review and meta-analysis to characterize the sensitivity and specificity of IPTT compared to traditional methods and to understand the potential screening value of IPTT.

Design： Systematic review and meta-analysis.

Data sources： PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedical Literature Database (CBM) up to April 16, 2020.

Methods: Stata version 15.1 software was used for analysis, and the screening value of IPTT in DPN was described using 10g-MF, NDS, Pin prick, 128Hz tuning fork, and ankle reflex as reference standards. Sensitivity, specificity, and other measures of accuracy of IPTT for screening DPN were pooled based on a quality effects model. The protocol was registered with PROSPERO (42020168420).

Results: Of the 441 records retrieved, seven studies were evaluated for the screening value of IPTT. Five studies with 10g-MF as the reference standard were included in the meta-analysis, and the pooled sensitivity and specificity were 0.78 (95 % CI 0.65–0.87) and 0.95(95 % CI 0.89–0.98), respectively, and AUC was 0.93. Compared with VPT, IPTT showed a sensitivity between 0.76 and 1, and a specificity between 0.90 and 0.97. Compared with NDS, IPTT showed a sensitivity between 0.53 and 1, and a specificity between 0.90 and 0.97. Compared with Pin prick, IPTT showed a

sensitivity and specificity of 0.8 and 0.88, respectively. Compared with 128Hz tuning fork, IPTT showed a sensitivity and specificity of 0.4 and 0.27, respectively. Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97.

Conclusions: IPTT shows a high degree of agreement with other commonly used screening tools for DPN screening. It can be used clinically, especially in remote areas and in primary medical institutions, and by self-monitoring patients. More high-quality studies are needed to assess and promote more effective screening practices.

Prospero: Registration Number is CRD (42020168420)

Strengths and limitations of this study

- This is the first meta-analysis to explore the potential screening value of IPTT in DPN.
- A quality effects model was used to achieve optimal error estimation in the data analysis.
- A Doi plots and Luis Furuya-Kanamori (LFK) index were used to assess publication bias.
- Although we systematically and comprehensively studied the current evidence of IPTT screening in DPN screening, the number of original studies was very limited, and the existing conclusions were based on these 7 original studies. Therefore, readers should therefore proceed with caution.

Keywords: Ipswich Touch Test, Diabetic peripheral neuropathy, Meta-analysis

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common long-term complication and the most important risk factor for the occurrence of diabetic foot ulcers (DFU).[1-4] DPN affects up to 50% of people with diabetes,[5,6] with chronic painful neuropathy affecting up to 26%.[7] In the early stage of DPN, the symptoms lack specificity, and about half of patients with diabetes cannot recognize the injury to the lower extremities.[8,9] Once the patient has symptoms such as limb numbness and pain, it signals that pathological changes have occurred in the peripheral nerves and have advanced into the

irreversible stage. If not treated promptly, serious tissue damage, such as foot ulcers, amputation, and even death, may occur.[10,11] Studies have shown that early screening and detection of peripheral neuropathy can not only slow down the DPN process, but also effectively prevent DFU.[12] Therefore, early screening and treatment of DPN is very important.

At present, the screening value of 10g monofilament (10g-MF), Vibration perception threshold (VPT), and 128Hz tuning fork in DPN has been widely recognized.[13] Compared with VPT and 128Hz tuning forks, 10g-MF is the most widely used screening tool because it is more simple, objective, and easy to carry, although it requires a calibration facility to confirm that the vertical pressure of the monofilament used when bending is 10g.[14-16] Commercially available 10g-MF devices exhibit significant variability within and between devices of different manufacturers and their actual bending force varies widely from their designated 10g value. When used they have a short service life where the instrument is within 10% of their initial bending force which is not usually the stated 10g of force.[17,18] Meanwhile, medical personnel are required to be trained before using the device, and screening is limited to hospitals or clinics. For clinics and communities in remote areas, medical personnel may lack the device or the training to screen patients for DPN, resulting in a missed opportunity for patients to receive the best treatment. In recent years, Dr. Rayman proposed the Ipswich Touch Test (IPTT), which only requires the physician's index finger. During this test, the patient is required to close their eyes while the physician lightly rests their finger on each of the patient's first, third, and fifth toes for 1 to 2 seconds. Patients are instructed to respond with a "yes" when they feel the physician's touch. Compared with the current methods, IPTT requires no equipment, is more convenient and effective, and can be performed by doctors, nurses, and even family caregivers after training.[19] IPTT can be applied to inpatients, outpatients, community patients, self-monitoring patients at home, and to areas lacking more advanced equipment.[20,21] Currently, IPTT has been applied in the United Kingdom, Spain, Brazil, and Saudi Arabia,[19,22-26] and was approved by the American Diabetes Association in 2015.[20] The 2019 guidelines of the International Working Group on the Diabetic Foot also suggest that IPTT should be used for DPN screening in patients with diabetes in the absence of 10g-MF.[27] Although these studies have achieved satisfactory results, they have not been widely promoted and applied globally.

Previous studies have reported differences in the results of the screening value of DPN. However, neither a meta-analysis nor a systematic review has been conducted on the screening value of IPTT.

In this study, we aimed to conduct a comprehensive and systematic literature review to systematically evaluate the potential screening value of IPTT in DPN, and provide evidence and guidance for the clinical application value of IPTT.

METHODS

The Joanna Briggs Institute (JBI) protocol[28] has been registered with PROSPERO, the International Prospective Register of Systematic Reviews hosted by the Centre for Reviews and Dissemination (Registration Number is CRD (42020168420). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[29].

Data Sources and Searches

We systematically searched PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, Chinese Biomedical Literature Database (CBM) for reports published before April 16, 2020. For included studies with insufficient data, we emailed the authors to ask if they would provide data for our study. With this strategy, we combined search terms for applied technique (Ipswich touch test, touch test, IPTT) and disease (Diabetic peripheral neuropathy, diabetic foot, diabetic foot ulcer, Diabetes Mellitus, diabetic complications). The study design and published language were not limited. In addition, we conducted a manual search, including searching through conference papers and gray literature, and the references of all included studies were examined. All search strategies were determined by multiple pre-searches, and the search formulas were adjusted according to the characteristics of each database. A detailed search strategy is provided in “Supplementary files 1”. All analyses were based on previously published studies; thus, no ethical approval and patient consent were required.

Inclusion and Exclusion Criteria

Previously published studies were included in this meta-analysis if: (1) the study examined the screening accuracy of the IPTT test for detecting DPN; (2) all the research subjects were patients

with diabetes, and; (3) IPTT was included as an index test. Studies were excluded from the meta-analysis if the studies had incomplete data sets or were other than original reports (commentaries/reviews). The age, sex, region, and race of the subjects were not restricted. The published language was not limited.

Data Extraction and Quality Assessment

We imported initial search records from databases into NoteExpress V3.2.0.7535 literature management software. Two reviewers independently screened titles and abstracts of all the included literature, following the inclusion and exclusion criteria. After screening the abstract, the full text was read in detail. Any discrepancies were resolved by discussion. The following information was extracted from the eligible studies: study characteristics (author, publication year, study period, country, reference standard, setting, operators), participant characteristics (sample number, range), and outcome indicators (sensitivity, specificity, true positive number (TP), false positive number (FP), false negative number (FN), true negative number (TN)). Missing data were supplemented by contacting authors wherever possible.

The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS), it is a methodological quality assessment scale, and includes 14 items[30]. Quality items were weighted equally with 1 point awarded for each of the 14 items. The quality score was then calculated by summing the points awarded for each question (maximum sum 14). This score was then normalized by dividing the sum by the highest score of the listed studies, thereby ranking the studies from 1 down to a minimum of 0.[31] Data extraction and quality assessment was performed independently by two reviewers. Differences were reconciled through discussion until a consensus was reached on the item in question.

Data Synthesis

We calculated sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and DOR, a value of pooled PLR greater than 10 and of pooled NLR less than 0.1 were noted as providing convincing diagnostic evidence. For each summary statistic, a 95% confidence interval

(95% CI) was computed, and the sensitivity, specificity, PLR, NLR, DOR and corresponding 95% CI were obtained using the quality effects model under the split component synthesis method framework.[32,33] Relevant studies have proven that the quality effects model is superior to the traditional random effects model.[34-36] The quality scores were used to redistribute inverse variance weights based on study deficiencies via the quality effects model,[37,38] and analyses were conducted using Stata, version15.1 (Stata Corp, College Station, TX).

Since the number of studies included affects the Q test, we used the I^2 statistic to evaluate the magnitude of heterogeneity since the value of the I^2 statistic will not change with the number of studies included and the results of heterogeneity test are more reliable, An $I^2 \geq 50\%$ indicates the existence of significant heterogeneity.[39,40] Publication bias was assessed with Doi plots and Luis Furuya-Kanamori (LFK) index, the Doi plot uses a rank-based measure (Z score) of precision (instead of the standard error) and plots it against the effect size, it can visualize asymmetry, and the LFK index quantifies the extent of Doi plot asymmetry by averaging half of the sum of the Z score plus the normalized effect size across the meta-analysis, which can detect and quantify the asymmetry in the Doi plots. The closer the value of the LFK index is to zero, the more symmetrical the Doi plot.[41] LFK index values outside the interval of -1 and +1 are deemed consistent with asymmetry.[41] Related studies have shown that these methods can markedly improve the ability of researchers to detect bias in a meta-analysis. [41]

Patient and public involvement

Since the data in this study were all from previously published studies, patients and the public were not involved in this research.

RESULTS

Study Selection

Our initial search resulted in a total of 441 records: 437 from database searching and four records from manual searches of references. After duplicates were removed, 242 records were identified, and 220 records were excluded as irrelevant. After reading the full-text articles, 7 studies met the

inclusion criteria (Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.). Two studies were excluded for lacking necessary data for meta-analysis. Finally, five studies with 6 datasets were included in the final meta-analysis, involving a total of 1162 patients.[22-26]

Characteristics and Quality of the Included Studies

The characteristics of the included studies are presented in Table 1. The 7 studies included a total of 1,510 participants with diabetes and were published between 2011 and 2020.[19,22-27] To explore the accuracy of IPTT in DPN screening, 10g-MF, VPT, NDS, pin prick, 128Hz tuning fork, and ankle reflex were used as the reference standard. The research setting included homes of patients, clinics, care centers, and outpatient centers, and the assessors included doctors, nurses, and family caregivers.

We assessed the methodological quality of the studies using QUADAS. The assessment results of the research methodological quality of each study are presented in Figures 2.[42]

Table 1. Basic characteristics of the included studies.

Study	Year	Country	n	Setting	Operators	Quality score(Qi)	Reference standard	TP	FP	FN	TN	Se(%)	Sp (%)
Sharma[22]	2012	UK	130	home	families	0.074	10g-MF	24	4	6	96	80.0	96.0
Sharma[23]	2014	UK	331	home	families	0.714	10g-MF	65	15	18	233	78.3	93.9
				clinic	doctors/ nurses	0.786	10g-MF	67	9	16	239	81.2	96.4
Amal Madanat[24]	2015	Saudi Arabia	351	care centers	doctors/ nurses	0.357	10g-MF	29	6	28	288	51.0	98.0
							VPT	48	24	9	270	85	92
							NDS	30	9	27	285	53	97
I.S, Basir[25]	2020	Spain	100	care centers	doctors/ nurses	0.429	10g- MF	4	30	1	65	80.0	68.0
							Pin prick	4	1	11	84	80.0	88.0
							Tuning fork 128Hz	2	3	69	26	40.0	27.0
							Ankle reflex	1	4	2	93	20.0	97.0
Dutra[26]	2020	Brasília	250	outpatient centre	doctors/ nurses	0.643	10g-MF	30	5	6	209	83.3	97.7
Rayman[19]	2011	UK	265	clinic	-	-	VPT	-	-	-	-	76.0	90.0
Bowling[27]	2012	UK	83	clinic	doctors/ nurses	-	VPT	-	-	-	-	100	96.6
							NDS	-	-	-	-	100	90.3

Se, Sensitivity; Sp, Specificity

Screening Accuracy

In the included studies, the researchers used a variety of different test methods as the standard to observe the sensitivity and specificity of IPTT for screening for DPN, such as 10g-MF, VPT, NDS, tuning fork 128Hz, and ankle reflex. The differences in the sensitivity and specificity of IPTT obtained by using different test methods as reference standards are presented. In general, when 10g-MF and VPT were used as reference standards, the sensitivity and specificity of IPTT were relatively high. For the 5 studies comprising 6 data pools that used 10g-MF as the reference standard, the sensitivity ranged from 51.0% - 83.3%, and the specificity ranged from 68.0 - 98.0%.[22-26] For the 3 studies that used VPT as a reference standard, the sensitivity ranged from 76.0 - 100.0%, and the specificity ranged from 90.0 - 96.6%. Using neuropathy disability scores (NDS) as the reference standard, the sensitivity of IPTT to be 0.53, and the specificity to be 0.97. Compared with the pin prick, the sensitivity and specificity of IPTT were 0.8 and 0.88, respectively.[24] Compared with 128Hz tuning fork, the sensitivity and specificity of IPTT were only 0.4 and 0.27, respectively.[25] Compared with ankle reflex, IPTT had a sensitivity of 0.2 and a specificity of 0.97(Table 1).[25]

Meta-analysis Results Using 10g-MF as the Reference Standard

Screening Accuracy

In the literature we retrieved, there were a total of five studies with IPTT as the target test and 10g-MF as the reference standard.[22-26] Among these five studies, one study contained two datasets because it was conducted at the patient's homes and in the clinic.[22] Therefore, six datasets were included to evaluate the overall effect of IPTT in the screening of DPN. [22-26] The combined sensitivity and specificity were 0.77 (95％CI 0.69–0.84) and 0.96 (95％CI 0.93–0.98), respectively.

The results show I - squared is 40.5%. In addition, the DOR was 75.24(39.90-141.89). The SROC analysis for the studies yielded an overall weighted area under the curve of 0.897(0.86-0.92) (Figure 3; Supplementary Files 2;Table 2).

Table 2. Meta-analysis of screening accuracy under the quality effect model

Variables	Se (95% CI)	Sp (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Pooled value	0.77(0.69-0.84)	0.96(0.93-0.98)	18.06 (10.75-30.36)	0.24(0.17-0.35)	75.24(39.90-141.89)	0.897(0.86-0.93)

Se, Sensitivity; Sp, Specificity; CI: Confidence Interval.

Publication Bias

Minor asymmetry was present in the Doi plot and the results of the LFK index also suggested minor negative asymmetry of the Doi plot (LFK index =-1.68). The findings might provide unequivocal evidence for publication bias, implying that studies with negative or equal outcomes are lacking. However, these findings might also be attributable to chance, given the few number of studies included in the analyses (Figure 4).

DISCUSSION

DPN is the most important risk factor for the occurrence of DFU and one of the more common chronic complications associated with diabetes. However, it is often ignored. Once the patient develops DPN, it is likely to cause diabetic foot ulcers, gangrene, and even amputation, and many patients experience numbness and tingling in their limbs. Early identification of DPN can greatly reduce the burden of chronic diseases on society. In this study, we systematically reviewed the relevant literature on the identification of DPN by IPTT. A total of 7 studies were included, involving 1,510 participants with diabetes to explore the value of IPTT screening. Previous studies have disputed the diagnostic value of IPTT, mainly due to the use of different test methods, such as VPT, NDS, pinprick, tuning fork 128Hz, and ankle reflex, as the reference standard, compared with NDS, acupuncture, 128Hz tuning fork, and ankle reflex, IPTT has higher screening accuracy when 10g-MF and VPT were used as the reference standard.[10,19,20] Basir et al. observed that when the 128Hz tuning fork was used as a reference standard, the sensitivity and specificity of IPTT were only 40% and 27%, respectively. This may be due to the lower predictive level of the tuning fork compared to the monofilament. However, Miller et al observed that combining a tuning fork with a monofilament would result in a more effective evaluation.[21] Regarding the quality of the current

studies, some studies lacked rigor in study design, such as the interval between target tests and unclear reference standard tests, and most studies failed to describe the reference methods in detail. The overall quality of the included studies was rated as low to medium quality.

Compared with 10g-MF, the results of the meta-analysis found the combined sensitivity and specificity of IPTT to be 0.77(95％CI 0.69-0.84) and 0.96(95％CI 0.93-0.98), respectively, and the AUC to be 0.897(95％CI 0.86-0.93). The results indicated that IPTT cannot well rule out DPN, but can confirm DPN effectively. In our study, the PLR and the NLR were 18.06 (95% CI 10.75-30.36) and 0.24(95% CI 0.17-0.35), respectively, it means that the ratio of the true positive rate to the false positive rate of IPTT screening for DPN is 18.06, and the ratio of false negative rate to true negative rate is 0.24. A DOR equal to 1 indicated that a test was unable to distinguish between patients with or without the disease. Our study yielded a DOR value of 75.24(95％CI 39.90-141.89), indicating that IPTT had good discrimination in patients with DPN. We also found that when VPT is used as a reference standard, IPTT shows a higher sensitivity and specificity. At present, 10g-MF and VPT are the most widely used clinical screening methods for DPN. Basir et al. explored the accuracy of using IPTT in detecting neuropathy in patients with small fiber and large fiber neuropathy, and found that there was no difference between IPTT and the gold standard, indicating that IPTT can be used as an alternative assessment method.[25] Therefore, the current evidence shows that IPTT has a high screening value for DPN and can be used for preliminary screening of DPN in areas lacking more advanced equipment.

Heterogeneity is an important factor of this meta-analysis.[43] In this study, we chose the quality effects model because it has been proven to be significantly better than the traditional random effects model and fixed effects model and attempts bias adjustment. When 10g-MF was used as the reference standard, the I^2 was only 40.5%, indicating there was good consistency among the five studies included in the meta-analysis. In addition, the existence of heterogeneity may be related to other factors, such as differences in research methodology, operators, or other factors. Due to the limited number of included studies, we did not analyze the heterogeneity through subgroup analysis

in this study. In terms of methodology, although we systematically and comprehensively studied the current evidence of using IPTT for DPN screening, the number of original studies is very limited, and the current conclusions are based only on these seven studies. Therefore, caution should be taken when generalizing these results. About using other test methods as the reference standard (except 10g-MF), we only described the relevant indicators as there were too few related studies to merge data. In addition, despite our efforts to conduct a thorough search for eligible studies, symmetry was detected. Thus, the pooled effect may have been overstated, this was also one of the limitations of our study.

Studies have shown that routine foot examinations and rapid risk stratification are often difficult to implement in busy primary care institutions. Additionally, the lack of awareness of standardized testing for DPN amongst healthcare professionals is a concern, which may be due to a shortage of material and personnel resources in primary care institutions. This is concerning because identifying foot neuropathy and the patients at risk for ulceration has been shown to prevent the incidence of foot ulcers.[44-46] IPTT is a new method for screening DPN that does not require any tools and can be carried out after minimal training. It is not affected by time, venue, or its operators.[20] The advancement of IPTT is of great significance for the early screening of DPN to impede the progression of diabetic foot ulcers, as it can be used to quickly and reliably screen and manage patients at high risk for ulceration, especially in remote areas or places lacking screening tools.[47,48] Kerry et al. reported that in the first year IPTT was introduced as a screening tool, the relative risk reduction (RRR) of DFU was 64%, and in the second year, the RRR was 70%, thereby reducing hospital-acquired foot ulcers in patients with diabetes by two-thirds and negating the excess risk associated with diabetes.[20,49-51] Meanwhile, it can effectively improve patients' disease-related knowledge, which plays a positive role in promoting the self-management of patients and their families. At the same time, IPTT has a predictive effect on diabetic foot ulcers and reduces delays in patient visits.[21] However, more thorough studies are needed for verification.

Most of the literature on IPTT is focused on screening tests and some commentary-type studies, and the number of studies is small. These studies were carried out in the United Kingdom, Spain, Brazil, and Saudi Arabia, and although they achieved satisfactory results, have not been carried out

globally. However, it has not been applied in developing countries such as China. China is a country with a large population and a relatively small number of medical personnel, especially in some remote areas where the medical allocation is in short supply. In these areas, the application and promotion of IPTT can effectively alleviate the challenges associated with the allocation of medical resources and play an important role in the management of patients with diabetes. IPTT has also recently been approved for use in a number of countries.[21,24-26] However, Kempegowda et al. reported that 88.4% of physicians are not familiar with IPTT. Therefore, we suggest that IPTT be further promoted amongst physicians and medical staff, especially in remote areas and areas lacking screening tools.[36] Future large-scale, high-quality, and multi-center studies on populations of different ethnicities will verify the potential applicability of IPTT alone or in combination with other DPN screening methods.

CONCLUSIONS

In summary, IPTT shows a high degree of agreement with commonly used screening tools for DPN, it can be used clinically, especially in remote areas and primary medical institutions, and self-monitoring patients. This is also the first meta-analysis of the accuracy of IPTT identification of DPN, and a systematic quantitative evaluation of its screening value, which can provide evidence for the clinical application of IPTT in the future. However, due to a limited number of studies of low or medium quality from limited geographical areas, more high-quality studies are needed to promote more effective screening practices.

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Author contributions

ZN conducted the database search, screened and extracted data for the meta-analysis, prepared extracted data for the procedures, and had primary responsibility in writing this article. LXY, ZJ and ZF performed statistical analysis and contributed to article screening, data collection and extraction. XJC, ZQH, and LJH contributed to the discussion and editing. XJC and CJR critically revised the draft manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Competing interests

The authors state that they have no conflict of interest.

Patient consent for publication

Not required. All analyses were conducted based on previously published studies. Accordingly, there was no patient or public involvement in this study. Ethical approval was not required since it was a systematic review of the published literature.

Data availability statement

Data are available in a public, open access repository. There are no data in this work. Data are available on reasonable request. Data can be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information.

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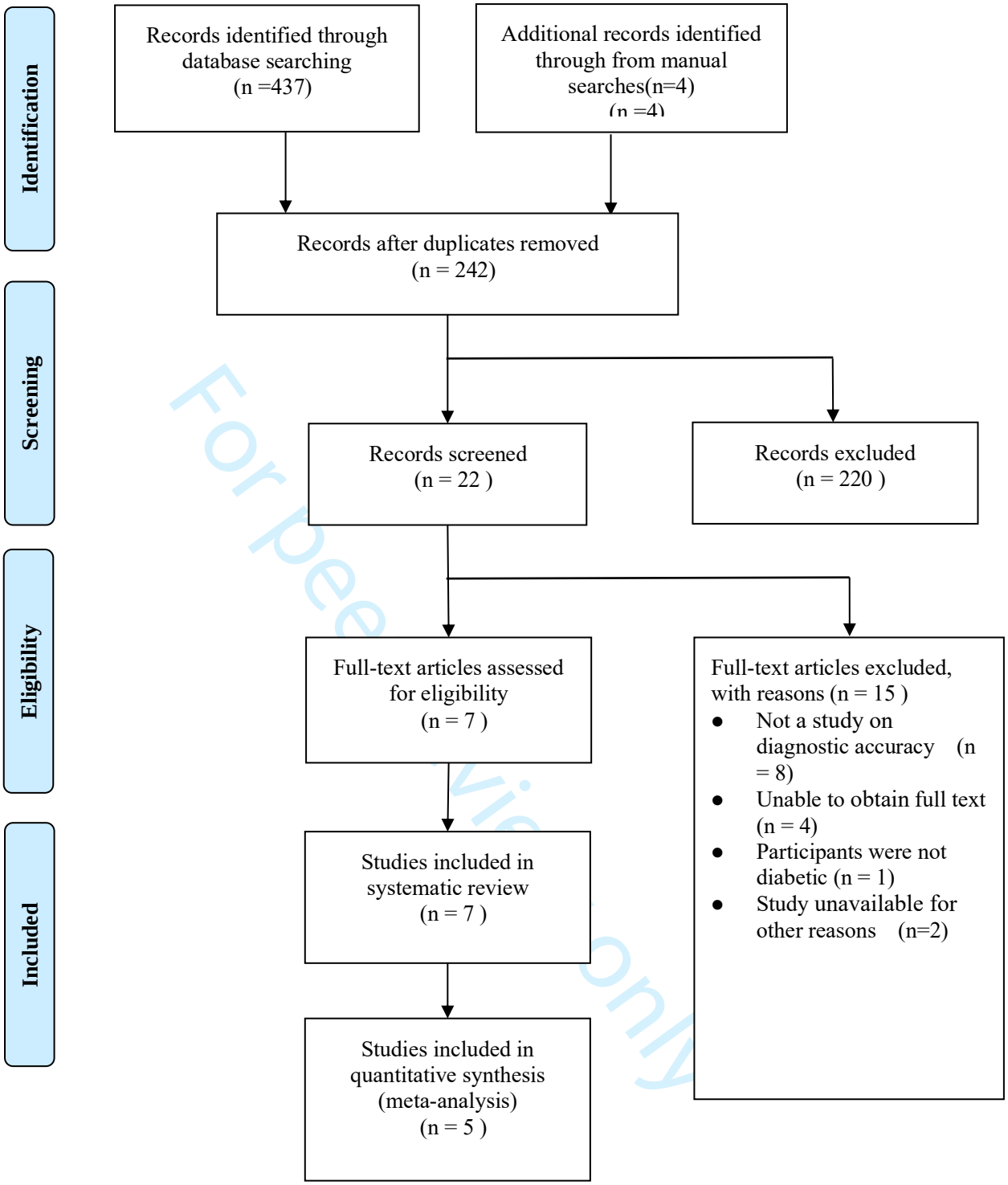

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2. Quality assessment of the included studies

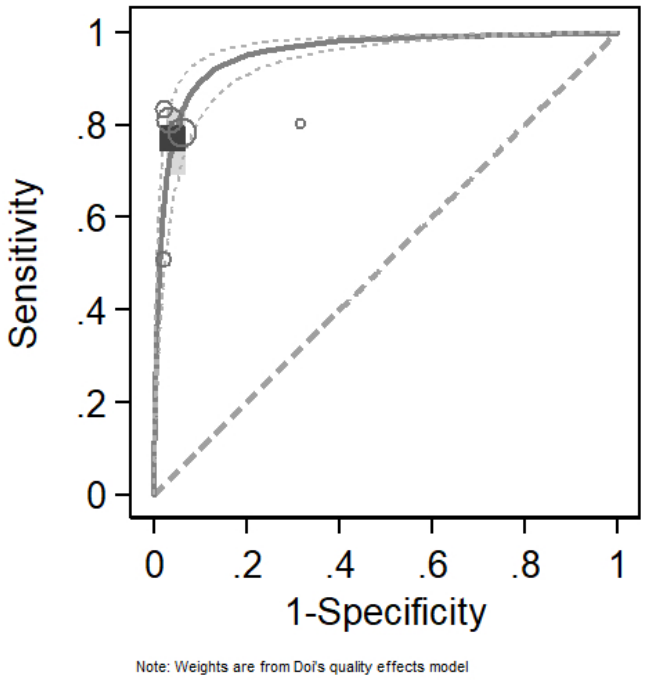

Figure 3. Sensitivity and specificity of IPTT in the diagnosis of DPN

255x185mm (72 x 72 DPI)

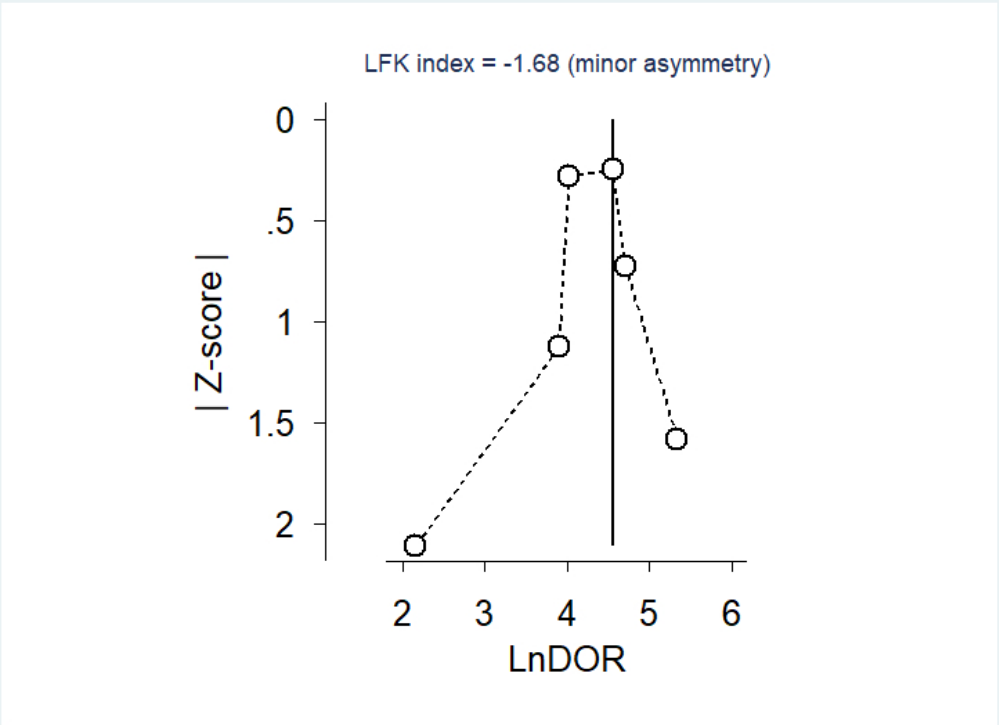

Figure 4. Doi plot and LFK index.

255x185mm (72 x 72 DPI)

Appendix S1

Search Strategy in PubMed, Embase, Cochrane Library, Web of Science, CNKI, CMB, Wanfang database.

PubMed Search Strategy

#1 Search: "Diabetes Mellitus"[Mesh] Sort by: Most Recent

#2 Search: ((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract])

#3 Search: "Diabetic Neuropathies"[Mesh] Sort by: Most Recent

#4 Search: ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR

(Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract])

#5 Search: "Diabetes Complications"[Mesh] Sort by: Most Recent

#6 Search:

#7 Search: "Diabetic Foot"[Mesh] Sort by: Most Recent

#8 Search: (((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])

#9 Search: ((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract])

#10 Search: (((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR (Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic

Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract]))

#11 Search: (((((((("Diabetes Mellitus"[Mesh]) OR (((((Diabetes[Title/Abstract]) OR (Diabetes, Type 2[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (Diabetes Mellitus, Type 1[Title/Abstract]))) OR ("Diabetic Neuropathies"[Mesh])) OR ((((((((((((((((((((((((((((Diabetic Neuropathy[Title/Abstract]) OR (Neuropathies, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathy[Title/Abstract])) OR (Autonomic Neuropathies, Diabetic[Title/Abstract])) OR (Diabetic Autonomic Neuropathies[Title/Abstract])) OR (Neuropathies, Diabetic Autonomic[Title/Abstract])) OR (Autonomic Neuropathy, Diabetic[Title/Abstract])) OR (Neuropathy, Diabetic Autonomic[Title/Abstract])) OR (Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathy[Title/Abstract])) OR

(Asymmetric Polyneuropathies, Diabetic[Title/Abstract])) OR (Asymmetric Polyneuropathy, Diabetic[Title/Abstract])) OR (Diabetic Asymmetric Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic Asymmetric[Title/Abstract])) OR (Polyneuropathy, Diabetic Asymmetric[Title/Abstract])) OR (Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Mononeuropathies[Title/Abstract])) OR (Mononeuropathies, Diabetic[Title/Abstract])) OR (Mononeuropathy, Diabetic[Title/Abstract])) OR (Diabetic Mononeuropathy Simplex[Title/Abstract])) OR (Diabetic Mononeuropathy Simplices[Title/Abstract])) OR (Mononeuropathy Simplex, Diabetic[Title/Abstract])) OR (Mononeuropathy Simplices, Diabetic[Title/Abstract])) OR (Simplex, Diabetic Mononeuropathy[Title/Abstract])) OR (Simplices, Diabetic Mononeuropathy[Title/Abstract])) OR (Diabetic Polyneuropathy[Title/Abstract])) OR (Diabetic Polyneuropathies[Title/Abstract])) OR (Polyneuropathies, Diabetic[Title/Abstract])) OR (Polyneuropathy, Diabetic[Title/Abstract]))) OR ("Diabetes Complications"[Mesh])) OR (((((((Diabetes-Related Complications[Title/Abstract]) OR (Diabetes Related Complications[Title/Abstract])) OR (Diabetes-Related Complication[Title/Abstract])) OR (Diabetic Complications[Title/Abstract])) OR (Diabetic Complication[Title/Abstract])) OR (Complications of Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus Complication[Title/Abstract])) OR (Diabetes Mellitus Complications[Title/Abstract]))) OR ("Diabetic Foot"[Mesh])) OR ((((Foot, Diabetic[Title/Abstract]) OR (Diabetic Feet[Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])))) AND (((ipswich touch test[Title/Abstract]) OR (touch test[Title/Abstract])) OR (IPTT[Title/Abstract]))

Embase Search Strategy

#1 'diabetes mellitus'/exp

#2 'diabetes, type 2':ab,ti OR 'type 2 diabetes mellitus':ab,ti OR 'diabetes mellitus, type ii':ab,ti OR 'diabetes mellitus, type 1':ab,ti

#3 #1 OR #2

#4 'diabetic neuropathy'/exp

#5 'diabetic neuropathy':ab,ti OR 'neuropathies, diabetic':ab,ti OR 'neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathy':ab,ti OR 'autonomic neuropathies, diabetic':ab,ti OR 'autonomic neuropathy, diabetic':ab,ti OR 'diabetic autonomic neuropathies':ab,ti OR 'neuropathies, diabetic autonomic':ab,ti OR 'neuropathy, diabetic autonomic':ab,ti OR 'symmetric diabetic proximal motor neuropathy':ab,ti OR 'asymmetric diabetic proximal motor neuropathy':ab,ti OR 'diabetic asymmetric polyneuropathy':ab,ti OR 'asymmetric polyneuropathies, diabetic':ab,ti OR 'asymmetric polyneuropathy, diabetic':ab,ti OR 'diabetic asymmetric polyneuropathies':ab,ti OR 'polyneuropathies, diabetic asymmetric':ab,ti OR 'polyneuropathy, diabetic asymmetric':ab,ti OR 'diabetic mononeuropathy':ab,ti OR 'diabetic mononeuropathies':ab,ti OR 'mononeuropathies, diabetic':ab,ti OR 'mononeuropathy, diabetic':ab,ti OR 'diabetic mononeuropathy simplex':ab,ti OR 'diabetic mononeuropathy simplices':ab,ti OR 'mononeuropathy simplex, diabetic':ab,ti OR 'mononeuropathy simplices, diabetic':ab,ti OR 'simplex, diabetic mononeuropathy':ab,ti OR 'simplices, diabetic mononeuropathy':ab,ti OR 'diabetic polyneuropathy':ab,ti OR 'diabetic polyneuropathies':ab,ti OR 'polyneuropathies, diabetic':ab,ti OR 'polyneuropathy, diabetic':ab,ti

#6 #4 OR #5

#7 'diabetic complication'/exp

#8 'diabetes complication':ab,ti OR 'diabetes-related complications':ab,ti OR 'diabetes related complications':ab,ti OR 'diabetes-related complication':ab,ti OR 'diabetic complications':ab,ti OR 'diabetic complication':ab,ti OR 'complications of diabetes mellitus':ab,ti OR 'diabetes mellitus complication':ab,ti OR 'diabetes mellitus complications':ab,ti

#9 #7 OR #8

#10 'diabetic foot'/exp

#11 'diabetic foot':ab,ti OR 'diabetic feet':ab,ti OR 'feet, diabetic':ab,ti OR 'foot ulcer,

diabetic':ab,ti OR 'foot ulcer':ab,ti

#12 #10 OR #11

#13 #3 OR #6 OR #9 OR #12

#14 'ipswich touch test':ab,ti OR 'touch test':ab,ti OR 'iptt':ab,ti

#15 #13 AND #14

Cochrane Library Search Strategy

#1 MeSH descriptor: [Diabetes Mellitus] explode all trees 31055

#2 (Diabetes):ti,ab,kw OR (Diabetes, Type 2):ti,ab,kw OR (Type 2 Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus, Type II):ti,ab,kw OR (Diabetes Mellitus, Type 1)

#3 MeSH descriptor: [Diabetic Neuropathies] explode all trees

#4 (Diabetic Neuropathy):ti,ab,kw OR (Neuropathies, Diabetic):ti,ab,kw OR (Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathy):ti,ab,kw OR (Autonomic Neuropathies, Diabetic):ti,ab,kw OR (Autonomic Neuropathy, Diabetic):ti,ab,kw OR (Diabetic Autonomic Neuropathies):ti,ab,kw OR (Neuropathies, Diabetic Autonomic):ti,ab,kw OR (Neuropathy, Diabetic Autonomic):ti,ab,kw OR (Symmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Asymmetric Diabetic Proximal Motor Neuropathy):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathy):ti,ab,kw OR (Asymmetric Polyneuropathies, Diabetic):ti,ab,kw OR (Asymmetric Polyneuropathy, Diabetic):ti,ab,kw OR (Diabetic Asymmetric Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic Asymmetric):ti,ab,kw OR (Polyneuropathy, Diabetic Asymmetric):ti,ab,kw OR (Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Mononeuropathies):ti,ab,kw OR (Mononeuropathies, Diabetic):ti,ab,kw OR (Mononeuropathy, Diabetic):ti,ab,kw OR (Diabetic Mononeuropathy Simplex):ti,ab,kw OR (Diabetic Mononeuropathy Simplices):ti,ab,kw OR (Mononeuropathy Simplex, Diabetic):ti,ab,kw OR (Mononeuropathy Simplices, Diabetic):ti,ab,kw OR (Simplex, Diabetic Mononeuropathy):ti,ab,kw OR

(Simplices, Diabetic Mononeuropathy):ti,ab,kw OR (Diabetic Polyneuropathy):ti,ab,kw OR (Diabetic Polyneuropathies):ti,ab,kw OR (Polyneuropathies, Diabetic):ti,ab,kw OR (Polyneuropathy, Diabetic):ti,ab,kw 3653

#5 MeSH descriptor: [Diabetes Complications] explode all trees

#6 (Diabetes-Related Complications):ti,ab,kw OR (Diabetes Related Complications):ti,ab,kw OR (Diabetes-Related Complication):ti,ab,kw OR (Diabetic Complications):ti,ab,kw OR (Diabetic Complication):ti,ab,kw OR (Complications of Diabetes Mellitus):ti,ab,kw OR (Diabetes Mellitus Complication):ti,ab,kw OR (Diabetes Mellitus Complications)

#7 MeSH descriptor: [Diabetic Foot] explode all trees

#8 (Diabetic Feet):ti,ab,kw OR (Feet, Diabetic):ti,ab,kw OR (Foot Ulcer, Diabetic)

#9 (ipswich touch test):ti,ab,kw OR (touch test):ti,ab,kw OR (IPTT)

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#11 #9 AND #10

Web of Science Search Strategy

#1 TS=(Diabetes Mellitus or Diabetes or Diabetes, Type 2 or Type 2 Diabetes Mellitus or Diabetes Mellitus, Type II or Diabetes Mellitus, Type 1)

#2 TS=(Diabetic Neuropathies or Diabetic Neuropathy or Neuropathies, Diabetic or Neuropathy, Diabetic or Diabetic Autonomic Neuropathy or Autonomic Neuropathies, Diabetic or Autonomic Neuropathy, Diabetic or Diabetic Autonomic Neuropathies or Neuropathies, Diabetic Autonomic or Neuropathy, Diabetic Autonomic or Symmetric Diabetic Proximal Motor Neuropathy or Asymmetric Diabetic Proximal Motor Neuropathy or Diabetic Asymmetric Polyneuropathy or Asymmetric Polyneuropathies, Diabetic or Asymmetric Polyneuropathy, Diabetic or Diabetic Asymmetric Polyneuropathies or

Polyneuropathies, Diabetic Asymmetric or Polyneuropathy, Diabetic Asymmetric or Diabetic Mononeuropathy or Diabetic Mononeuropathies or Mononeuropathies, Diabetic or Mononeuropathy, Diabetic or Diabetic Mononeuropathy Simplex or Diabetic Mononeuropathy Simplices or Mononeuropathy Simplex, Diabetic or Mononeuropathy Simplices, Diabetic or Simplex, Diabetic Mononeuropathy or Simplices, Diabetic Mononeuropathy or Diabetic Polyneuropathy or Diabetic Polyneuropathies or Polyneuropathies, Diabetic or Polyneuropathy, Diabetic)

#3 TS=(Diabetes Complications or Diabetes Complication or Diabetes-Related Complications or Diabetes Related Complications or Diabetes-Related Complication or Diabetic Complications or Diabetic Complication or Complications of Diabetes Mellitus or Diabetes Mellitus Complication or Diabetes Mellitus Complications)

#4 TS=(Diabetic Foot or Foot, Diabetic or Diabetic Feet or Feet, Diabetic or Foot Ulcer, Diabetic)

#5 #4 OR #3 OR #2 OR #1

#6 TS=(ipswich touch test or touch test or IPTT)

#7 #6 AND #5

China National Knowledge Infrastructure (CNKI) Search Strategy

检索式 A: (((主题=糖尿病 或者 题名=糖尿病 或者 v_subject=中英文扩展(糖尿病) 或者 title=中英文扩展(糖尿病)) 或者 (主题=糖尿病足 或者 题名=糖尿病足 或者 v_subject=中英文扩展(糖尿病足) 或者 title=中英文扩展(糖尿病足))) 或者 ((主题=糖尿病周围神经病变 或者 题名=糖尿病周围神经病变 或者 v_subject=中英文扩展(糖尿病周围神经病变) 或者 title=中英文扩展(糖尿病周围神经病变)) 或者 (主题=糖尿病并发症 或者 题名=糖尿病并发症 或者 v_subject=中英文扩展(糖尿病并发症) 或者 title=中英文扩展(糖尿病并发症)))) 并且 (((((主题=中英文扩展(touch test) 或者 题名=中英文扩展(touch test) 或者 v_subject=touch test 或者 title=touch test) 或者 (主题=中英文扩展(Ipswich Touch Test) 或者 题名=中英文扩展(Ipswich Touch Test) 或者

v_subject=Ipswich Touch Test 或者 title=Ipswich Touch Test)) 或者 ((主题=伊普斯维奇触摸测试 或者 题名=伊普斯维奇触摸测试 或者 v_subject=中英文扩展(伊普斯维奇触摸测试) 或者 title=中英文扩展(伊普斯维奇触摸测试)) 或者 (主题=中英文扩展(IPTT) 或者 题名=中英文扩展(IPTT) 或者 v_subject=IPTT 或者 title=IPTT))) 或者 ((关键词=轻触 或者 keyword=中英文扩展(轻触)) 或者 (关键词=轻触测试 或者 keyword=中英文扩展(轻触测试)))) 或者 ((题名=触摸 或者 Title=中英文扩展(触摸)) 或者 (题名=触摸测试 或者 Title=中英文扩展(触摸测试)))) (模糊匹配)

Wan Fang Database Search Strategy

主题:((糖尿病)+主题:(糖尿病足)+主题:(糖尿病周围神经病变)+全部:(糖尿病并发症))*主题:((touch test)+主题:(IPTT)+主题:(Ipswich Touch Test)+全部:(伊普斯维奇触摸测试))

China Biology Medicine disc (CBM) Search Strategy

#1 "糖尿病"[不加权:扩展]

#2 "糖尿病足"[常用字段:智能]

#3 "糖尿病神经病变"[常用字段:智能]

#4 "糖尿病并发症"[常用字段:智能]

#5 (#4) OR (#3) OR (#2) OR (#1)

#6 "touch"[常用字段:智能] AND "test"[常用字段:智能]

#7 "IPTT"[常用字段:智能]

#8 "Ipswich"[常用字段:智能] AND "Touch"[常用字段:智能] AND "Test"[常用字段:智能]

#9 "伊普斯维奇触摸测试"[常用字段:智能]

#10 "轻触"[常用字段:智能]

#11 "轻触测试"[常用字段:智能]

#12 "触摸"[常用字段:智能]

#13 "触摸测试"[常用字段:智能]

#14 (#13) OR (#12) OR (#11) OR (#10) OR (#9) OR (#8) OR (#7) OR (#6)

#15 (#14) AND (#5)

```
. diagma tp fp fn tn, qe(qi)

Input form: TP FP FN TN assumed
Note: Weights are from Doi's quality effects model
Studies included: 6
Participants included: 1493
Prevalence of disease: 19.7%
Heterogeneity (I-squared): 40.5%
Pub bias (LFK index): -1.7, minor asymmetry
```

	Estimate	95% Conf.	Interval
Sens	.77	.688	.836
Spec	.957	.928	.975
LR+	18.064	10.748	30.358
LR-	.24	.167	.346
DOR	75.239	39.898	141.887
AUC	.897	.863	.923

The results of sensitivity and specificity of IPTT in the diagnosis of DPN

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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